

AMIDE COMPOUNDS HAVING MCH-ANTAGONISTIC ACTIVITY AND MEDICAMENTS COMPRISING THESE COMPOUNDS

The present invention relates to new amide compounds, the physiologically acceptable salts thereof as well as their use as MCH antagonists and their use in preparing a pharmaceutical preparation which is suitable for the prevention and/or treatment of symptoms and/or diseases caused by MCH or causally connected with MCH in some other way. The invention also relates to the use of a compound according to the invention for influencing eating behaviour and for reducing body weight and/or for preventing any increase in body weight in a mammal. It further relates to compositions and medicaments containing a compound according to the invention and processes for preparing them.

Background to the Invention

15 The intake of food and its conversion in the body is an essential part of life for all living creatures. Therefore, deviations in the intake and conversion of food generally lead to problems and also illness. The changes in the lifestyle and nutrition of humans, particularly in industrialised countries, have promoted obesity 20 in recent decades. In affected people, obesity leads directly to restricted mobility and a reduction in the quality of life. There is the additional factor that obesity often leads to other diseases such as, for example, diabetes, dyslipidaemia, high blood pressure, arteriosclerosis and coronary heart disease. Moreover, high body weight alone puts an increased strain on the support and mobility apparatus, 25 which can lead to chronic pain and diseases such as arthritis or osteoarthritis. Thus, obesity is a serious health problem for society.

30 The term obesity means an excess of adipose tissue. In this connection, obesity is fundamentally to be seen as the increased level of fatness which leads to a health risk. In the last analysis it is not precisely possible to draw a distinction between normal individuals and those suffering from obesity, but the health risk

accompanying obesity is presumed to rise continuously as the level of fatness increases. For simplicity's sake, in the present invention, individuals with a Body Mass Index (BMI), which is defined as the body weight measured in kilograms divided by the height (in metres) squared, above a value of 25 and more particularly above 30 are preferably regarded as suffering from obesity.

Apart from physical activity and a change in nutrition, there is currently no convincing treatment option for effectively reducing body weight. However, as obesity is a major risk factor in the development of serious and even life-threatening diseases, it is all the more important to have access to pharmaceutical active substances for the prevention and/or treatment of obesity. One approach which has been proposed very recently is the therapeutic use of MCH antagonists (cf. *inter alia* WO 01/21577, WO 01/82925).

10 Melanin-concentrating hormone (MCH) is a cyclic neuropeptide consisting of 19 amino acids. It is synthesised predominantly in the hypothalamus in mammals and from there travels to other parts of the brain by the projections of hypothalamic neurones. Its biological activity is mediated in humans through two different G-protein-coupled receptors (GPCRs) from the family of rhodopsin-related GPCRs, namely the MCH receptors 1 and 2 (MCH-1R, MCH-2R).

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Investigations into the function of MCH in animal models have provided good indications for a role of the peptide in regulating the energy balance, i.e. changing metabolic activity and food intake [1,2]. For example, after intraventricular administration of MCH in rats, food intake was increased compared with control animals. Additionally, transgenic rats which produce more MCH than control animals, when given a high-fat diet, responded by gaining significantly more weight than animals without an experimentally altered MCH level. It was also found that there is a positive correlation between phases of increased desire for food and the quantity of MCH mRNA in the hypothalamus of rats. However, experiments with MCH knock-out mice are particularly important in showing the

function of MCH. Loss of the neuropeptide results in lean animals with a reduced fat mass, which take in significantly less food than control animals.

The anorectic effects of MCH are mediated in rodents through the G_{Vs}-coupled
5 MCH-1R [3-6]. Unlike primates, ferrets and dogs, no second receptor has hitherto been found in rodents. After losing the MCH-1R, knock-out mice have a lower fat mass, an increased energy conversion and, when fed on a high fat diet, do not put on weight, compared with control animals. Another indication of the importance of the MCH-MCH-1R system in regulating the energy balance results from
10 experiments with a receptor antagonist (SNAP-7941) [3]. In long term trials the animals treated with the antagonist lose significant amounts of weight.

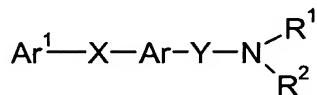
In addition to its anorectic effect, the MCH-1R antagonist SNAP-7941 also achieves additional anxiolytic and antidepressant effects in behavioural
15 experiments on rats [3]. Thus, there are clear indications that the MCH-MCH-1R system is involved not only in regulating the energy balance but also in affectivity.

Literature:

1. Qu, D., et al., *A role for melanin-concentrating hormone in the central regulation of feeding behaviour*. Nature, 1996. **380**(6571): p. 243-7.
20
2. Shimada, M., et al., *Mice lacking melanin-concentrating hormone are hypophagic and lean*. Nature, 1998. **396**(6712): p. 670-4.
3. Borowsky, B., et al., *Antidepressant, anxiolytic and anorectic effects of a melanin-concentrating hormone-1 receptor antagonist*. Nat Med, 2002. **8**(8):
25 p. 825-30.
4. Chen, Y., et al., *Targeted disruption of the melanin-concentrating hormone receptor-1 results in hyperphagia and resistance to diet-induced obesity*. Endocrinology, 2002. **143**(7): p. 2469-77.
5. Marsh, D.J., et al., *Melanin-concentrating hormone 1 receptor-deficient mice are lean, hyperactive, and hyperphagic and have altered metabolism*. Proc
30 Natl Acad Sci U S A, 2002. **99**(5): p. 3240-5.

6. Takekawa, S., et al., *T-226296: A novel, orally active and selective melanin-concentrating hormone receptor antagonist*. Eur J Pharmacol, 2002. **438**(3): p. 129-35.

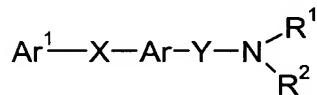
5 In the patent literature certain amine compounds are proposed as MCH antagonists. Thus, WO 01/21577 (Takeda) describes compounds of formula



wherein Ar¹ denotes a cyclic group , X denotes a spacer, Y denotes a bond or a spacer, Ar denotes an aromatic ring which may be fused with a non-aromatic ring, 10 R¹ and R² independently of one another denote H or a hydrocarbon group, while R¹ and R² together with the adjacent N atom may form an N-containing hetero ring and R² with Ar may also form a spirocyclic ring, R together with the adjacent N atom and Y may form an N-containing hetero ring, as MCH antagonists for the treatment of obesity.

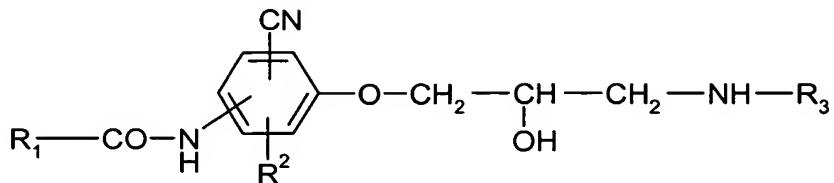
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Moreover WO 01/82925 (Takeda) also describes compounds of formula



wherein Ar¹ denotes a cyclic group , X and Y represent spacer groups, Ar denotes an optionally substituted fused polycyclic aromatic ring, R¹ and R² independently 20 of one another represent H or a hydrocarbon group, while R¹ and R² together with the adjacent N atom may form an N-containing heterocyclic ring and R² together with the adjacent N atom and Y may form an N-containing hetero ring, as MCH antagonists for the treatment of obesity, *inter alia*.

In EP 073 016 A1 (Boehringer Ingelheim) 1-aryloxy-3-alkylamino-2-propanols of general formula



wherein R₁ may represent aryloxyalkylene, *inter alia*, are proposed for use as
5 cardiac or coronary therapeutic agents or for lowering blood pressure. However,
there is no mention of these compounds having an MCH-antagonistic activity.

US 3,994,900 mentions *inter alia* n-(4-alkoxy-phenyl)-3-phenyl-acrylamides, n-(4-alkylthio-phenyl)-3-phenyl-acrylamides, n-(4-alkylsulphinyl-phenyl)-3-phenyl-
10 acrylamidse and n-(4-alkylsulphonyl-phenyl)-3-phenyl-acrylamides as starting materials for synthesising dihydroquinolinone derivatives.

DE 1088955 lists *inter alia* the compounds N-[4-(2-diethylamino-ethoxy)-phenyl]-3-phenyl-acrylamide and N-[4-(2-diethylamino-ethoxy)-phenyl]-3-phenyl-
15 propionamide.

WO 00/06153, which proposes compounds with a CCR5 receptor activity, mentions *inter alia* the compound 3-(3,4-dichloro-phenyl)-N-[3-(2-diisopropylamino-ethoxy)-4-methoxy-phenyl]-acrylamide.
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FR 1176918 mentions the compounds (N-[4-(2-morpholin-4-yloxy)-phenyl]-3-phenyl-propionamide) and N-[4-(2-diethylamino-ethoxy)-phenyl]-3-phenyl-propionamide.

25 In the article by A. P. Tamiz et al., J. Med. Chem. 42 (17), 1999, 3412-3420, the compound (3-(4-chloro-phenyl)-N-{2-[4-(2-diethylamino-ethoxy)-phenyl]-ethyl}-acrylamide) is mentioned.

In DE 3016827, which relates to compounds having an effect on the cardiovascular system, the compounds N-{2-[3-(4-{2-[2-(4-chloro-phenoxy)-acetylamino]-ethyl}-phenoxy)-2-hydroxy-propylamino]-ethyl}-isobutyramide, cyclopentanecarboxylic acid {2-[3-(4-{2-[2-(4-chloro-phenoxy)-acetylamino]-ethyl}-phenoxy)-2-hydroxy-propylamino]-ethyl}-amide and 2-(4-chloro-phenoxy)-N-(2-{4-[2-hydroxy-3-(2-phenylacetylamino-ethylamino)-propoxy]-phenyl}-ethyl)-acetamide *inter alia* are mentioned on page 55.

Aim of the invention

10 The aim of the present invention is to discover new amide compounds, particularly those which have an activity as MCH antagonists.

A further aim of the invention is to provide new amide compounds which make it possible to influence the eating behaviour of mammals and in particular achieve a reduction in body weight and/or prevent an increase in body weight in mammals.

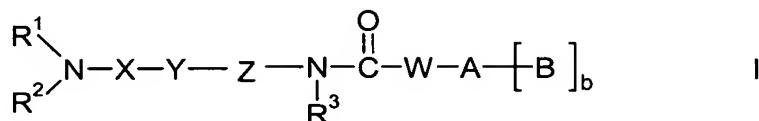
The present invention further sets out to provide new pharmaceutical compositions which are suitable for the prevention and/or treatment of symptoms and/or diseases caused by MCH or otherwise causally connected to MCH. In particular, 20 the aim of this invention is to provide pharmaceutical compositions for the treatment of metabolic disorders such as obesity and/or diabetes as well as diseases and/or disorders which are associated with obesity and diabetes. Other objectives of the present invention are concerned with demonstrating advantageous uses of the compounds according to the invention. The invention 25 also sets out to provide a process for preparing the amide compounds according to the invention. Other aims of the present invention will be immediately apparent to the skilled man from the foregoing remarks and those that follow.

Subject matter of the invention

A first object of the present invention comprises amide compounds of general formula I

Amide compounds of general formula I

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wherein

10 R^1, R^2 independently of one another denote H, a C_{1-8} -alkyl or C_{3-7} -cycloalkyl group optionally substituted by the group R^{11} , while a $-\text{CH}_2-$ group in position 3 or 4 of a 5-, 6- or 7-membered cycloalkyl group may be replaced by $-\text{O}-$, $-\text{S}-$, $-\text{NH}-$, $-\text{N}(\text{C}_{1-4}\text{-alkyl})-$ or $-\text{N}(\text{CO-O-C}_{1-4}\text{-alkyl})-$, or a phenyl or pyridinyl group optionally mono- or polysubstituted by the group R^{12} and/or monosubstituted by nitro, or

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R^1 and R^2 form a C_{2-8} -alkylene bridge wherein

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- one or two $-\text{CH}_2-$ groups may be replaced independently of one another by $-\text{CH}=\text{N}-$ or $-\text{CH}=\text{CH}-$ and/or
- one or two $-\text{CH}_2-$ groups may be replaced independently of one another by $-\text{O}-$, $-\text{S}-$, $-\text{SO}-$, $-(\text{SO}_2)-$, $-\text{C}=\text{N}-\text{O}-\text{R}^{18}-$, $-\text{CO}-$, $-\text{C}(\text{=CH}_2)-$ or $-\text{NR}^{13}-$ in such a way that heteroatoms are not directly connected to one another,

25

while in the above-defined alkylene bridge one or more H atoms may be replaced by R^{14} , and

while the above-defined alkylene bridge may be substituted by one or

two identical or different carbo- or heterocyclic groups Cy in such a way that the bond between the alkylene bridge and the group Cy is formed

- via a single or double bond,
- via a common C atom forming a spirocyclic ring system,
- via two common, adjacent C and/or N atoms forming a fused bicyclic ring system or
- via three or more C and/or N atoms forming a bridged ring system,

5 R³ denotes H, C₁₋₆-alkyl, C₃₋₇-cycloalkyl or C₃₋₇-cycloalkyl-C₁₋₄-alkyl ,

10

X denotes a C₁₋₈-alkylene bridge wherein

- a -CH₂- group may be replaced by -CH=CH- or -C≡C- and/or
- one or two -CH₂- groups may be replaced independently of one another by -O-, -S-, -(SO)-, -(SO₂)-, -CO- or -NR⁴- in such a way that in each case two O, S or N atoms or an O and an S atom are not directly connected to one another,

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while the bridge X may be attached to R¹ including the N atom attached to R¹ and X forming a heterocyclic group, while the bridge X may additionally also be attached to R², including the N-atom attached to R² and X, forming a heterocyclic group, and

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25 two C atoms or one C and one N atom of the alkylene bridge may be joined together by an additional C₁₋₄-alkylene bridge, and

25

a C atom may be substituted by R¹⁰ and/or one or two C atoms in each case may be substituted with one or two identical or different substituents selected from C₁₋₆-alkyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, C₃₋₇-cycloalkyl, C₃₋₇-cycloalkyl-C₁₋₃-alkyl, C₄₋₇-cycloalkenyl and C₄₋₇-cycloalkenyl-C₁₋₃-alkyl, while two alkyl and/or alkenyl substituents may be joined together, forming a carbocyclic ring system, and

W is selected from among $-CR^{6a}R^{6b}-O-$, $-CR^{7a}=CR^{7c}-$, $-CR^{6a}R^{6b}-NR^{8}-$,
 $-CR^{7a}R^{7b}-CR^{7c}R^{7d}-$ and $-NR^{8}-CR^{6a}R^{6b}-$,

5 Z denotes a single bond, C₁₋₄-alkylene, wherein two adjacent C atoms may be joined together with an additional C₁₋₄-alkylene bridge,
10 while a C atom of the alkylene bridge may be substituted with R¹⁰ and/or one or two C atoms independently of one another may be substituted with one or two identical or different C₁₋₆-alkyl groups, while two alkyl groups may be joined together, forming a carbocyclic ring, and

Y denotes one of the meanings given for Cy,
15 while R¹ may be attached to Y including the group X and the N atom attached to R¹ and X , forming a heterocyclic group fused to Y, and/or
20 X may be attached to Y forming a carbo- or heterocyclic group fused to Y, and

A denotes one of the meanings given for Cy,
B denotes one of the meanings given for Cy,
25 b denotes the value 0 or 1,

Cy denotes a carbo- or heterocyclic group selected from one of the following meanings
30 - a saturated 3- to 7-membered carbocyclic group,
- an unsaturated 4- to 7-membered carbocyclic group,
- a phenyl group,

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- a saturated 4- to 7-membered or unsaturated 5- to 7-membered heterocyclic group with an N, O or S atom as heteroatom,
- a saturated or unsaturated 5- to 7-membered heterocyclic group with two or more N atoms or with one or two N atoms and an O or S atom as heteroatoms,
- an aromatic heterocyclic 5- or 6-membered group with one or more identical or different heteroatoms selected from N, O and/or S,

10

while the above-mentioned 4-, 5-, 6- or 7-membered groups may be attached via two common, adjacent C atoms fused to a phenyl or pyridine ring, and

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in the above-mentioned 5-, 6- or 7-membered groups one or two non-adjacent -CH₂- groups may be replaced independently of one another by a -CO-, -C(=CH₂)-, -(SO)- or -(SO₂)- group, and

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the above-mentioned saturated 6- or 7-membered groups may also be present as bridged ring systems with an imino, N-(C₁₋₄-alkyl)-imino, methylene, C₁₋₄-alkyl-methylene or di-(C₁₋₄-alkyl)-methylene bridge, and

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the above-mentioned cyclic groups may be mono- or polysubstituted at one or more C atoms with R²⁰, in the case of a phenyl group they may also additionally be monosubstituted with nitro, and/or one or more NH groups may be substituted with R²¹,

R⁴ has one of the meanings given for R¹⁷, C₂₋₆-alkenyl or C₃₋₆-alkynyl,

R^{6a}, R^{6b} denotes H, C₁₋₄-alkyl or CF₃,

30 R^{7a}, R^{7b},

	R^{7c}, R^{7d}	denotes H, F, C ₁₋₄ -alkyl or CF ₃ ,
	R^8	denotes H, C ₁₋₄ -alkyl, C ₃₋₇ -cycloalkyl or C ₃₋₇ -cycloalkyl-C ₁₋₃ -alkyl,
5	R^{10}	denotes hydroxy, ω -hydroxy-C ₁₋₃ -alkyl, C ₁₋₄ -alkoxy, ω -(C ₁₋₄ -alkoxy)-C ₁₋₃ -alkyl, carboxy, C ₁₋₄ -alkoxycarbonyl, amino, C ₁₋₄ -alkyl-amino, di-(C ₁₋₄ -alkyl)-amino, cyclo-C ₃₋₆ -alkyleneimino, amino-C ₁₋₃ -alkyl, C ₁₋₄ -alkyl-amino-C ₁₋₃ -alkyl, di-(C ₁₋₄ -alkyl)-amino-C ₁₋₃ -alkyl, cyclo-C ₃₋₆ -alkyleneimino-C ₁₋₃ -alkyl, amino-C ₁₋₃ -alkoxy, C ₁₋₄ -alkyl-amino-C ₁₋₃ -alkoxy, di-(C ₁₋₄ -alkyl)-amino-C ₁₋₃ -alkoxy or cyclo-C ₃₋₆ -alkyleneimino-C ₁₋₃ -alkoxy, aminocarbonyl, C ₁₋₄ -alkyl-aminocarbonyl, di-(C ₁₋₄ -alkyl)-aminocarbonyl or cyclo-C ₃₋₆ -alkyleneimino-carbonyl,
10	R^{11}	denotes C ₂₋₆ -alkenyl, C ₂₋₆ -alkynyl, R ¹⁵ -O, R ¹⁵ -O-CO, R ¹⁵ -CO-O,
15		R ¹⁶ R ¹⁷ N, R ¹⁸ R ¹⁹ N-CO or Cy,
	R^{12}	has one of the meanings given for R ²⁰ ,
20	R^{13}	has one of the meanings given for R ¹⁷ , with the exception of carboxy,
25	R^{14}	denotes halogen, C ₁₋₆ -alkyl, C ₂₋₆ -alkenyl, C ₂₋₆ -alkynyl, R ¹⁵ -O, R ¹⁵ -O-CO, R ¹⁵ -CO, R ¹⁵ -CO-O, R ¹⁶ R ¹⁷ N, R ¹⁸ R ¹⁹ N-CO, R ¹⁵ -O-C ₁₋₃ -alkyl, R ¹⁵ -O-CO-C ₁₋₃ -alkyl, R ¹⁵ -O-CO-NH, R ¹⁵ -SO ₂ -NH, R ¹⁵ -O-CO-NH-C ₁₋₃ -alkyl-, R ¹⁵ -SO ₂ -NH-C ₁₋₃ -alkyl-, R ¹⁵ -CO-C ₁₋₃ -alkyl, R ¹⁵ -CO-O-C ₁₋₃ -alkyl, R ¹⁶ R ¹⁷ N-C ₁₋₃ -alkyl, R ¹⁸ R ¹⁹ N-CO-C ₁₋₃ -alkyl or Cy-C ₁₋₃ -alkyl,
	R^{15}	denotes H, C ₁₋₄ -alkyl, C ₃₋₇ -cycloalkyl, C ₃₋₇ -cycloalkyl-C ₁₋₃ -alkyl, phenyl, phenyl-C ₁₋₃ -alkyl, pyridinyl or pyridinyl-C ₁₋₃ -alkyl,
30	R^{16}	denotes H, C ₁₋₆ -alkyl, C ₃₋₇ -cycloalkyl, C ₃₋₇ -cycloalkyl-C ₁₋₃ -alkyl, C ₄₋₇ -cycloalkenyl, C ₄₋₇ -cycloalkenyl-C ₁₋₃ -alkyl, ω -hydroxy-C ₂₋₃ -alkyl, ω -(C ₁₋

C_{1-4} -alkoxy)- C_{2-3} -alkyl, amino- C_{2-6} -alkyl, C_{1-4} -alkyl-amino- C_{2-6} -alkyl, di-(C_{1-4} -alkyl)-amino- C_{2-6} -alkyl or cyclo- C_{3-6} -alkyleneimino- C_{2-6} -alkyl,

R^{17} has one of the meanings given for R^{16} or denotes
 5 phenyl, phenyl- C_{1-3} -alkyl, pyridinyl, dioxolan-2-yl, -CHO,
 C_{1-4} -alkylcarbonyl, carboxy, hydroxycarbonyl- C_{1-3} -alkyl,
 C_{1-4} -alkoxycarbonyl, C_{1-4} -alkoxycarbonyl- C_{1-3} -alkyl,
 C_{1-4} -alkylcarbonylamino- C_{2-3} -alkyl, N-(C_{1-4} -alkylcarbonyl)-N-(C_{1-4} -alkyl)-
 10 amino- C_{2-3} -alkyl, C_{1-4} -alkylsulphonyl, C_{1-4} -alkylsulphonylamino- C_{2-3} -alkyl
 or N-(C_{1-4} -alkylsulphonyl)-N(C_{1-4} -alkyl)-amino- C_{2-3} -alkyl

R^{18} , R^{19} independently of one another denote H or C_{1-6} -alkyl,
 15 R^{20} denotes halogen, hydroxy, cyano, C_{1-6} -alkyl, C_{2-6} -alkenyl, C_{2-6} -alkynyl,
 C_{3-7} -cycloalkyl, C_{3-7} -cycloalkyl- C_{1-3} -alkyl, hydroxy- C_{1-4} -alkyl, R^{22} - C_{1-3} -
 alkyl or one of the meanings given for R^{22} ,

R^{21} denotes C_{1-4} -alkyl, ω -hydroxy- C_{2-3} -alkyl, ω - C_{1-4} -alkoxy- C_{2-6} -alkyl, ω - C_{1-4} -
 20 alkyl-amino- C_{2-6} -alkyl, ω -di-(C_{1-4} -alkyl)-amino- C_{2-6} -alkyl, ω -cyclo- C_{3-6} -
 alkyleneimino- C_{2-6} -alkyl, phenyl- C_{1-3} -alkyl, C_{1-4} -alkyl-carbonyl,
 C_{1-4} -alkoxy-carbonyl or C_{1-4} -alkylsulphonyl,

R^{22} denotes phenyl- C_{1-3} -alkoxy, OHC, HO-N=HC, C_{1-4} -alkoxy-N=HC, C_{1-4} -
 25 alkoxy, C_{1-4} -alkylthio, carboxy, C_{1-4} -alkylcarbonyl, C_{1-4} -alkoxycarbonyl,
 aminocarbonyl, C_{1-4} -alkylaminocarbonyl, di-(C_{1-4} -alkyl)-aminocarbonyl,
 cyclo- C_{3-6} -alkyl-amino-carbonyl, cyclo- C_{3-6} -alkyleneimino-carbonyl,
 cyclo- C_{3-6} -alkyleneimino- C_{2-4} -alkyl-aminocarbonyl, phenyl-amino-
 carbonyl, C_{1-4} -alkyl-sulphonyl, C_{1-4} -alkyl-sulphanyl, C_{1-4} -alkyl-
 30 sulphonylamino, amino, C_{1-4} -alkylamino, di-(C_{1-4} -alkyl)-amino, C_{1-4} -alkyl-
 carbonyl-amino, cyclo- C_{3-6} -alkyleneimino, phenyl- C_{1-3} -alkylamino or

N-(C₁₋₄-alkyl)-phenyl-C₁₋₃-alkylamino, acetylamino, propionylamino, phenylcarbonylamino, phenylcarbonylmethylamino, hydroxy-alkylaminocarbonyl, (4-morpholinyl)carbonyl, (1-pyrrolidinyl)carbonyl, (1-piperidinyl)carbonyl, (hexahydro-1-azepinyl)carbonyl, (4-methyl-1-piperazinyl)carbonyl, methylenedioxy, aminocarbonylamino or alkylaminocarbonylamino,

while in the above-mentioned groups and residues, especially in A, B, W, X, Y, Z, R¹ to R⁴, R^{6a}, R^{6b}, R^{7a}, R^{7b}, R^{7c}, R^{7d}, R⁸, R¹⁰ to R²², in particular, in each case one or more C atoms may additionally be mono- or polysubstituted by F and/or in each case one or two C atoms may additionally be monosubstituted by Cl or Br independently of one another and/or in each case one or more phenyl rings may additionally, independently of one another, have one, two or three substituents selected from among F, Cl, Br, I, C₁₋₄-alkyl, C₁₋₄-alkoxy, difluoromethyl, trifluoromethyl, hydroxy, amino, C₁₋₃-alkylamino, di-(C₁₋₃-alkyl)-amino, acetylamino, aminocarbonyl, cyano, difluoromethoxy, trifluoromethoxy, amino-C₁₋₃-alkyl, C₁₋₃-alkylamino-C₁₋₃-alkyl- and di-(C₁₋₃-alkyl)-amino-C₁₋₃-alkyl and/or may be monosubstituted by nitro, and

the H atom of any carboxy group present or an H atom bonded to an N atom may each be replaced by a group which can be cleaved in vivo,

the tautomers, the diastereomers, the enantiomers, the mixtures thereof and the salts thereof,

with the following provisos (M1), (M2) and (M3)

(M1) in the event that Y denotes phenylene substituted with -CN,

X denotes -CH₂-CH(OH)-CH₂-O-, Z denotes a single bond, R¹ denotes a straight-chain or branched alkyl group with 1 to 10 C atoms and R² and R³ represent H, then W does not represent -CR^{6a}R^{6b}-O-,

(M2) in the event that W denotes -CH=CH- and Y denotes a phenylene group and

5 Z is a single bond, then the bridges X and Z at the phenylene ring of the
group Y are in the para position to one another and at least one of the
following conditions is met:

- (a) the group Y meaning phenylene is at least monosubstituted,
- (b) b has the value 0 and the group A is at least disubstituted,
- (c) b has the value 1;

10 (M3) the following individual compounds are not included:

N-[4-(2-diethylamino-ethoxy)-phenyl]-3-phenyl-propionamide,
N-[4-(2-morpholin-4-ylethoxy)-phenyl]-3-phenyl-propionamide,
3-(4-chloro-phenyl)-N-{2-[4-(2-diethylamino-ethoxy)-phenyl]-ethyl}-
acrylamide,
15 N-{2-[3-(4-{2-[2-(4-chloro-phenoxy)-acetylamino]-ethyl}-phenoxy)-2-hydroxy-
propylamino]-ethyl}-isobutyramide,
cyclopentanecarboxylic acid {2-[3-(4-{2-[2-(4-chloro-phenoxy)-acetylamino]-
ethyl}-phenoxy)-2-hydroxy-propylamino]-ethyl}-amide,
20 2-(4-chloro-phenoxy)-N-(2-{4-[2-hydroxy-3-(2-phenylacetylamino-
ethylamino)-propoxy]-phenyl}-ethyl)-acetamide.

The invention also relates to the compounds in the form of the individual optical
isomers, mixtures of the individual enantiomers or racemates, in the form of the
tautomers and in the form of the free bases or the corresponding acid addition
25 salts with pharmacologically safe acids. The subject of the invention also includes
the compounds according to the invention, including the salts thereof, wherein one
or more hydrogen atoms are replaced by deuterium.

This invention also includes the physiologically acceptable salts of the amide
30 compounds according to the invention as described above and hereinafter.

This invention also relates to compositions containing at least one amide compound according to the invention and/or a salt according to the invention optionally together with one or more physiologically acceptable excipients.

5 Also covered by this invention are pharmaceutical compositions containing at least one amide compound according to the invention and/ or a salt according to the invention optionally together with one or more inert carriers and/or diluents.

This invention also relates to the use of at least one amide compound according to
10 the invention and/or a salt according to the invention, including the compounds excluded by provisos (M1), (M2) and (M3) , for influencing the eating behaviour of a mammal.

The invention further relates to the use of at least one amide compound according
15 to the invention and/or a salt according to the invention, including the compounds excluded by provisos (M1), (M2) and (M3) , for reducing the body weight and/ or for preventing an increase in the body weight of a mammal.

The invention also relates to the use of at least one amide compound according to
20 the invention and/or a salt according to the invention, including the compounds excluded by provisos (M1), (M2) and (M3) , for preparing a pharmaceutical composition with an MCH receptor-antagonistic activity, particularly with an MCH-1 receptor-antagonistic activity.

25 This invention also relates to the use of at least one amide compound according to the invention and/or a salt according to the invention, including the compounds excluded by provisos (M1), (M2) and (M3) , for preparing a pharmaceutical composition which is suitable for the prevention and/or treatment of symptoms and/or diseases which are caused by MCH or are otherwise causally connected
30 with MCH.

A further object of this invention is the use of at least one amide compound according to the invention and/or a salt according to the invention, including the compounds excluded by provisos (M1), (M2) and (M3) , for preparing a pharmaceutical composition which is suitable for the prevention and/or treatment
5 of metabolic disorders and/or eating disorders, particularly obesity, bulimia, bulimia nervosa, cachexia, anorexia, anorexia nervosa and hyperphagia

The invention also relates to the use of at least one amide compound according to the invention and/or a salt according to the invention, including the compounds
10 excluded by provisos (M1), (M2) and (M3) , for preparing a pharmaceutical composition which is suitable for the prevention and/or treatment of diseases and/or disorders associated with obesity, particularly diabetes, especially type II diabetes, complications of diabetes including diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, insulin resistance, pathological glucose
15 tolerance, encephalorrhagia, cardiac insufficiency, cardiovascular diseases, particularly arteriosclerosis and high blood pressure, arthritis and gonitis.

In addition the present invention relates to the use of at least one amide compound according to the invention and/or a salt according to the invention,
20 including the compounds excluded by provisos (M1), (M2) and (M3) , for preparing a pharmaceutical composition which is suitable for the prevention and/or treatment of hyperlipidaemia, cellulitis, fat accumulation, malignant mastocytosis, systemic mastocytosis, emotional disorders, affective disorders, depression, anxiety, sleep disorders, reproductive disorders, sexual disorders, memory
25 disorders, epilepsy, forms of dementia and hormonal disorders.

The invention also relates to the use of at least one amide compound according to the invention and/or a salt according to the invention, including the compounds excluded by provisos (M1), (M2) and (M3) , for preparing a pharmaceutical
30 composition which is suitable for the prevention and/or treatment of urinary

problems, such as for example urinary incontinence, overactive bladder, urgency, nycturia and enuresis.

The invention further relates to processes for preparing for preparing a

5 pharmaceutical composition according to the invention, characterised in that at least one amide compound according to the invention and/ or a salt according to the invention is incorporated in one or more inert carriers and/or diluents by a non-chemical method.

10 The invention also relates to a pharmaceutical composition containing a first active substance which is selected from the amide compounds according to the invention and/or the corresponding salts, including the compounds excluded by provisos (M1), (M2) and (M3), as well as a second active substance which is selected from the group consisting of active substances for the treatment of diabetes, active

15 substances for the treatment of diabetic complications, active substances for the treatment of obesity, preferably other than MCH antagonists, active substances for the treatment of high blood pressure, active substances for the treatment of hyperlipidaemia, including arteriosclerosis, active substances for the treatment of arthritis, active substances for the treatment of anxiety states and active

20 substances for the treatment of depression, optionally together with one or more inert carriers and/or diluents.

Detailed Description of the invention

Unless otherwise specified the groups, residues and substituents, particularly A, B,
25 W, X, Y, Z, R¹ to R⁴, R^{6a}, R^{6b}, R^{7a}, R^{7b}, R^{7c}, R^{7d}, R⁸, R¹⁰ to R²², and index b, have the meanings given hereinbefore.

According to one embodiment the groups R¹, R², X, Z, b, R¹⁰, R¹⁴, R¹⁵, R¹⁷, R²⁰, R²¹, R²² have the following meanings:

R ¹ , R ²	independently of one another denote H, a C ₁₋₈ -alkyl or C ₃₋₇ -cycloalkyl group optionally substituted by the group R ¹¹ , or a phenyl group optionally mono- or polysubstituted by the group R ¹² and/or monosubstituted by nitro, or
5	R ¹ and R ² form a C ₂₋₈ -alkylene bridge wherein
10	<ul style="list-style-type: none"> - one or two -CH₂- groups independently of one another may be replaced by -CH=N- or -CH=CH- and/or - one or two -CH₂- groups independently of one another may be replaced by -O-, -S-, -CO-, -C(=CH₂)-or -NR¹³- so that heteroatoms are not directly connected to one another, <p>while in the alkylene bridge defined above one or more H atoms may be replaced by R¹⁴, and</p>
15	while the alkylene bridge defined hereinbefore may be substituted with one or two identical or different carbo- or heterocyclic groups Cy so that the bond between the alkylene bridge and the group Cy is made
20	<ul style="list-style-type: none"> - via a single or double bond, - via a common C atom forming a spirocyclic ring system, - via two common adjacent C and/or N atoms forming a fused bicyclic ring system or - via three or more C and/or N atoms forming a bridged ring system,
25	X denotes a C ₁₋₈ -alkylene bridge wherein
30	<ul style="list-style-type: none"> - a -CH₂- group may be replaced by -CH=CH- or -C≡C- and/or - one or two -CH₂- groups may be replaced independently of one another by -O-, -S-, -(SO)-, -(SO₂)-, -CO- or -NR⁴- in such a way

that in each case two O, S or N atoms or an O and an S atom are not directly joined together,

5 while the bridge X may be connected to R¹ including the N atom attached to R¹ and X forming a heterocyclic group, and

two C atoms or a C and an N atom of the alkylene bridge may be joined together by an additional C₁₋₄-alkylene bridge, and

10 a C atom may be substituted by R¹⁰ and/or one or two C atoms in each case may be substituted by one or two identical or different C₁₋₆-alkyl groups, and

15 Z denotes a single bond, C₁₋₄-alkylene, wherein two adjacent C atoms may be joined together by an additional C₁₋₄-alkylene bridge,

while a C atom of the alkylene bridge may be substituted by R¹⁰ and/or one or two C atoms independently of one another may be substituted by one or two identical or different C₁₋₆-alkyl groups, and

20 b has the value 0,

R¹⁰ denotes hydroxy, ω-hydroxy-C₁₋₃-alkyl, C₁₋₄-alkoxy, ω-(C₁₋₄-alkoxy)-C₁₋₃-alkyl, amino, C₁₋₄-alkyl-amino, di-(C₁₋₄-alkyl)-amino, cyclo-C₃₋₆-alkyleneimino, amino-C₁₋₃-alkyl, C₁₋₄-alkyl-amino-C₁₋₃-alkyl, di-(C₁₋₄-alkyl)-amino-C₁₋₃-alkyl, cyclo-C₃₋₆-alkyleneimino-C₁₋₃-alkyl, amino-C₁₋₃-alkoxy, C₁₋₄-alkyl-amino-C₁₋₃-alkoxy, di-(C₁₋₄-alkyl)-amino-C₁₋₃-alkoxy or cyclo-C₃₋₆-alkyleneimino-C₁₋₃-alkoxy,

30 R¹⁴ denotes halogen, C₁₋₆-alkyl, R¹⁵-O, R¹⁵-O-CO, R¹⁵-CO, R¹⁵-CO-O, R¹⁶R¹⁷N, R¹⁸R¹⁹N-CO, R¹⁵-O-C₁₋₃-alkyl-, R¹⁵-O-CO-C₁₋₃-alkyl,

R^{15} -CO-C₁₋₃-alkyl, R^{15} -CO-O-C₁₋₃-alkyl, $R^{16}R^{17}$ N-C₁₋₃-alkyl,
 $R^{18}R^{19}$ N-CO-C₁₋₃-alkyl or Cy-C₁₋₃-alkyl,

5 R^{15} denotes H, C₁₋₄-alkyl, C₃₋₇-cycloalkyl, C₃₋₇-cycloalkyl-C₁₋₃-alkyl,
 phenyl or phenyl-C₁₋₃-alkyl,

10 R^{17} has one of the meanings given for R^{16} or denotes
 phenyl, phenyl-C₁₋₃-alkyl, C₁₋₄-alkylcarbonyl,
 hydroxycarbonyl-C₁₋₃-alkyl, C₁₋₄-alkylcarbonylamino-C₂₋₃-alkyl,
 N-(C₁₋₄-alkylcarbonyl)-N-(C₁₋₄-alkyl)-amino-C₂₋₃-alkyl,
 C₁₋₄-alkylsulphonyl, C₁₋₄-alkylsulphonylamino-C₂₋₃-alkyl or
 N-(C₁₋₄-alkylsulphonyl)-N(C₁₋₄-alkyl)-amino-C₂₋₃-alkyl,

15 R^{20} denotes halogen, hydroxy, cyano, C₁₋₆-alkyl, C₃₋₇-cycloalkyl, C₃₋₇-cycloalkyl- C₁₋₃-alkyl, hydroxy-C₁₋₄-alkyl, R^{22} -C₁₋₃-alkyl or one of the
 meanings given for R^{22} ,

20 R^{21} denotes C₁₋₄-alkyl, ω -hydroxy-C₂₋₃-alkyl, ω -C₁₋₄-alkoxy-C₂₋₆-alkyl,
 ω -C₁₋₄-alkyl-amino-C₂₋₆-alkyl, ω -di-(C₁₋₄-alkyl)-amino-C₂₋₆-alkyl, ω -cyclo-C₃₋₆-alkyleneimino-C₂₋₆-alkyl, phenyl, phenyl-C₁₋₃-alkyl, C₁₋₄-alkyl-carbonyl, carboxy, C₁₋₄-alkoxy-carbonyl or C₁₋₄-alkylsulphonyl,

25 R^{22} denotes phenyl, phenyl-C₁₋₃-alkoxy, C₁₋₄-alkoxy, C₁₋₄-alkylthio, carbonyl, C₁₋₄-alkylcarbonyl, C₁₋₄-alkoxycarbonyl, aminocarbonyl,
 C₁₋₄-alkylaminocarbonyl, di-(C₁₋₄-alkyl)-aminocarbonyl,
 cyclo-C₃₋₆-alkyleneimino-carbonyl, C₁₋₄-alkyl-sulphonyl, C₁₋₄-alkyl-sulphanyl, C₁₋₄-alkyl-sulphonylamino, amino, C₁₋₄-alkylamino, di-(C₁₋₄-alkyl)-amino, cyclo-C₃₋₆-alkyleneimino, phenyl-C₁₋₃-alkylamino or
 N-(C₁₋₄-alkyl)-phenyl-C₁₋₃-alkylamino, acetylamino, propionylamino,
 phenylcarbonylamino, phenylcarbonylmethylamino, hydroxy-alkylaminocarbonyl, (4-morpholinyl)carbonyl, (1-pyrrolidinyl)carbonyl,

(1-piperidinyl)carbonyl, (hexahydro-1-azepinyl)carbonyl, (4-methyl-1-piperazinyl)carbonyl, methylenedioxy, aminocarbonylamino or alkylaminocarbonylamino,

5 while the groups and residues R^3 , R^4 , R^{6a} , R^{6b} , R^{7a} , R^{7b} , R^{7c} , R^{7d} , R^8 , R^{11} , R^{12} , R^{16} , R^{18} , R^{19} , W, Y, A, Cy have the meanings given hereinbefore.

Preferably the group R^3 denotes H or C_{1-4} -alkyl, particularly preferably H or methyl, particularly H.

10

If R^1 and R^2 are not joined together via an alkylene bridge, R^1 and R^2 independently of one another preferably represent a C_{1-8} -alkyl or C_{3-7} -cycloalkyl group optionally substituted by the group R^{11} , while a - CH_2 - group in position 3 or 4 of a 5-, 6- or 7-membered cycloalkyl group may be replaced by -O-, -S- or -NH-, -N(C_{1-4} -alkyl)- or -N(CO-O- C_{1-4} -alkyl)-, or a phenyl or pyridinyl group optionally mono- or polysubstituted by the group R^{12} and/or monosubstituted by nitro, and one of the groups R^1 and R^2 may also represent H.

15

Preferably the groups R^1 , R^2 independently of one another represent H, C_{1-6} -alkyl, C_{3-7} -cycloalkyl, C_{3-7} -cycloalkyl- C_{1-3} -alkyl, ω -hydroxy- C_{2-3} -alkyl, ω -(C_{1-4} -alkoxy)- C_{2-3} -alkyl, C_{1-4} -alkoxy-carbonyl- C_{1-4} -alkyl, carboxyl- C_{1-4} -alkyl, amino- C_{2-4} -alkyl, C_{1-4} -alkyl-amino- C_{2-4} -alkyl, di-(C_{1-4} -alkyl)-amino- C_{2-4} -alkyl, cyclo- C_{3-6} -alkyleneimino- C_{2-4} -alkyl, pyrrolidin-3-yl, N-(C_{1-4} -alkyl)-pyrrolidinyl, pyrrolidinyl- C_{1-3} -alkyl, N-(C_{1-4} -alkyl)-pyrrolidinyl- C_{1-3} -alkyl, piperidinyl, N-(C_{1-4} -alkyl)-piperidinyl, piperidinyl- C_{1-3} -alkyl, N-(C_{1-4} -alkyl)-piperidinyl- C_{1-3} -alkyl, phenyl, phenyl- C_{1-3} -alkyl, pyridyl or pyridyl- C_{1-3} -alkyl, while in the above-mentioned groups and residues one or more C atoms may be mono- or polysubstituted by F and/or one or two C atoms may independently of one another be monosubstituted by Cl or Br, and the phenyl or pyridyl group may be mono- or polysubstituted by the group R^{12} as hereinbefore defined and/or may be monosubstituted by nitro. Preferred substituents of the above-mentioned phenyl or pyridyl groups are selected from the group F, Cl, Br, I,

cyano, C₁₋₄-alkyl, C₁₋₄-alkoxy, difluoromethyl, trifluoromethyl, hydroxy, amino, C₁₋₃-alkylamino, di-(C₁₋₃-alkyl)-amino, acetylamino, aminocarbonyl, difluoromethoxy, trifluoromethoxy, amino-C₁₋₃-alkyl, C₁₋₃-alkylamino-C₁₋₃-alkyl- and di-(C₁₋₃-alkyl)-amino-C₁₋₃-alkyl, while a phenyl group may also be monosubstituted by nitro.

Particularly preferred definitions of the groups R¹ and/or R² are selected from among C₁₋₆-alkyl, C₃₋₇-cycloalkyl, C₃₋₇-cycloalkyl-C₁₋₃-alkyl, ω-hydroxy-C₂₋₃-alkyl, ω-(C₁₋₄-alkoxy)-C₂₋₃-alkyl, C₁₋₄-alkoxy-carbonyl-C₁₋₄-alkyl, carboxyl-C₁₋₄-alkyl, while one of the groups R¹ and R² may also represent H.

Particularly preferably, at least one of the groups R¹, R², and most preferably both groups, has a meaning other than H.

If R¹ and R² form an alkylene bridge, it is preferably a C₃₋₇-alkylene bridge wherein

- a -CH₂- group not adjacent to the N atom of the R¹R²N group may be replaced by -CH=N- or -CH=CH- and/or
- a -CH₂- group which is preferably not adjacent to the N atom of the R¹R²N group, may be replaced by -O-, -S-, -C(=N-O-R¹⁸)-, -CO-, -C(=CH₂)- or -NR¹³- , most preferably by -O-, -S- or -NR¹³- , in such a way that heteroatoms are not directly connected to one another,

while in the alkylene bridge defined above one or more H atoms may be replaced by R¹⁴, and

the alkylene bridge defined hereinbefore may be substituted by a carbo- or heterocyclic group Cy in such a way that the bond between the alkylene bridge and the group Cy is made

- via a single or double bond,
- via a common C atom forming a spirocyclic ring system,

- via two common adjacent C and/or N atoms forming a fused bicyclic ring system or
- via three or more C and/or N atoms forming a bridged ring system.

5 Also preferably, R¹ and R² form an alkylene bridge in such a way that R¹R²N- denotes a group selected from azetidine, pyrrolidine, piperidine, azepan, 2,5-dihydro-1H-pyrrole, 1,2,3,6-tetrahydro-pyridine, 2,3,4,7-tetrahydro-1H-azepine, 2,3,6,7-tetrahydro-1H-azepine, piperazine, wherein the free imine function is substituted by R¹³, piperidin-4-one, piperidin-4-one-oxime, piperidin-4-one-O-C₁₋₄-alkyl-oxime, morpholine and thiomorpholine, while according to the general definition of R¹ and R² one or more H atoms may be replaced by R¹⁴, and/ or the above-mentioned groups may be substituted by one or two identical or different carbo- or heterocyclic groups Cy in a manner specified according to the general definition of R¹ and R². Particularly preferred groups Cy are C₃₋₇-cycloalkyl, aza-C₄₋₇- cycloalkyl, particularly cyclo-C₃₋₆-alkyleneimino, as well as 1-C₁₋₄-alkyl-aza-C₄₋₇-cycloalkyl.

10 The C₂₋₈-alkylene bridge formed by R¹ and R² wherein -CH₂- groups may be replaced as specified may be substituted by one or two identical or different carbo- or heterocyclic groups Cy as described.

15 If the alkylene bridge is linked to a group Cy via a single bond, Cy is preferably selected from among C₃₋₇-cycloalkyl, cyclo-C₃₋₆-alkyleneimino, 1H-imidazol, thieryl and phenyl.

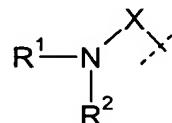
20 If the alkylene bridge is linked to a group Cy via a common C atom forming a spirocyclic ring system, Cy is preferably selected from among C₃₋₇-cycloalkyl, aza-C₄₋₈-cycloalkyl, oxa-C₄₋₈-cycloalkyl, 2,3-dihydro-1H-quinazolin-4-one.

25

If the alkylene bridge is linked to a group Cy via two common adjacent C and/or N atoms forming a fused bicyclic ring system, Cy is preferably selected from among C₄₋₇-cycloalkyl, phenyl, thienyl.

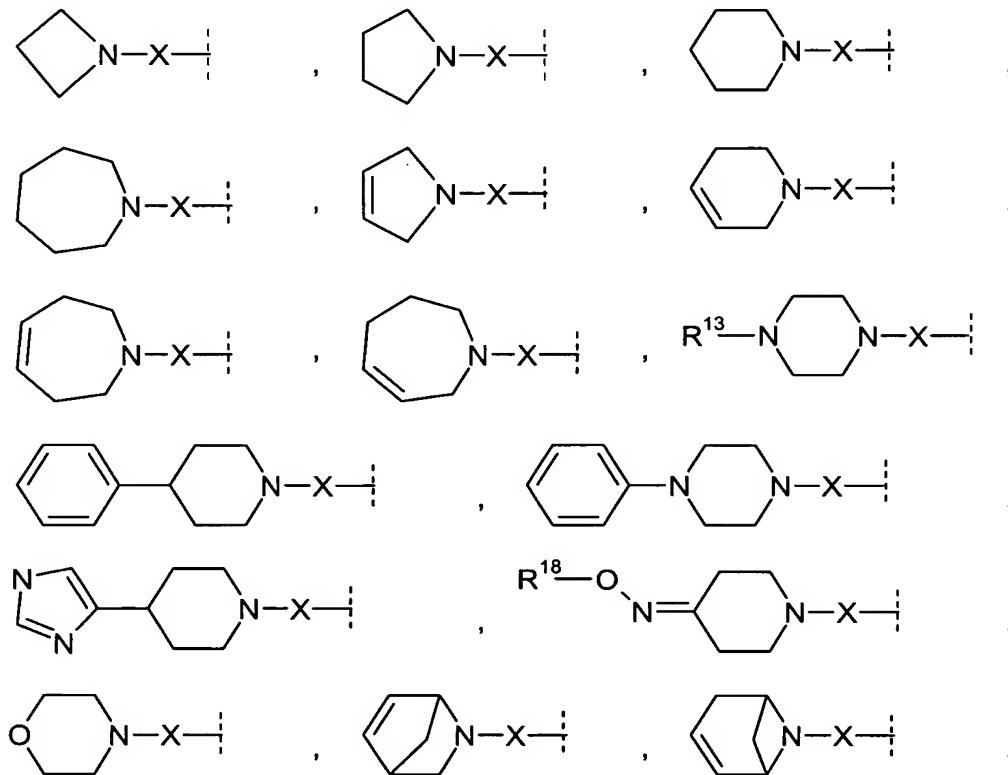
5 If the alkylene bridge is linked to a group Cy via three or more C and/or N atoms forming a bridged ring system, Cy preferably denotes C₄₋₈-cycloalkyl or aza-C₄₋₈-cycloalkyl.

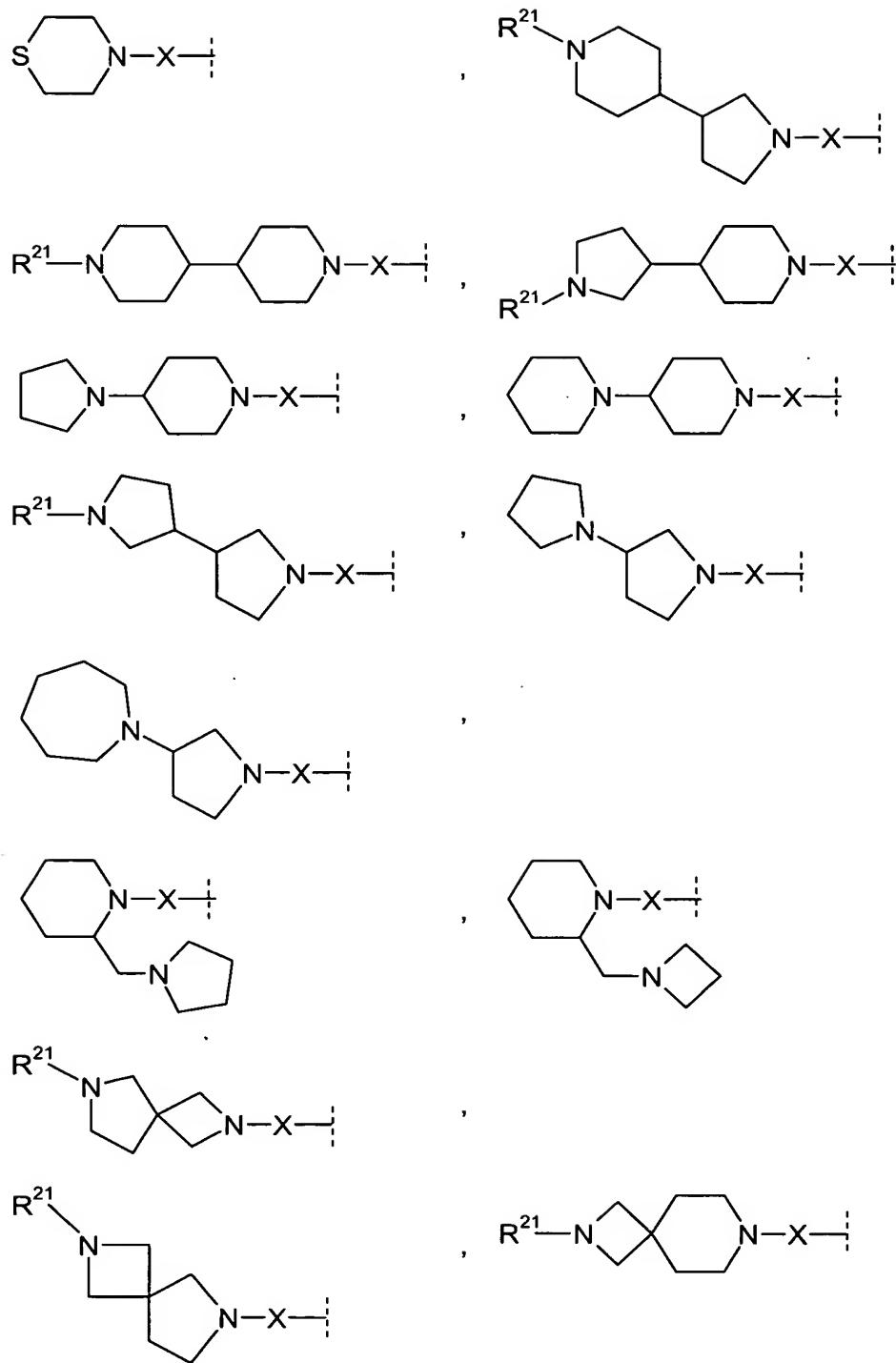
Preferably, the group

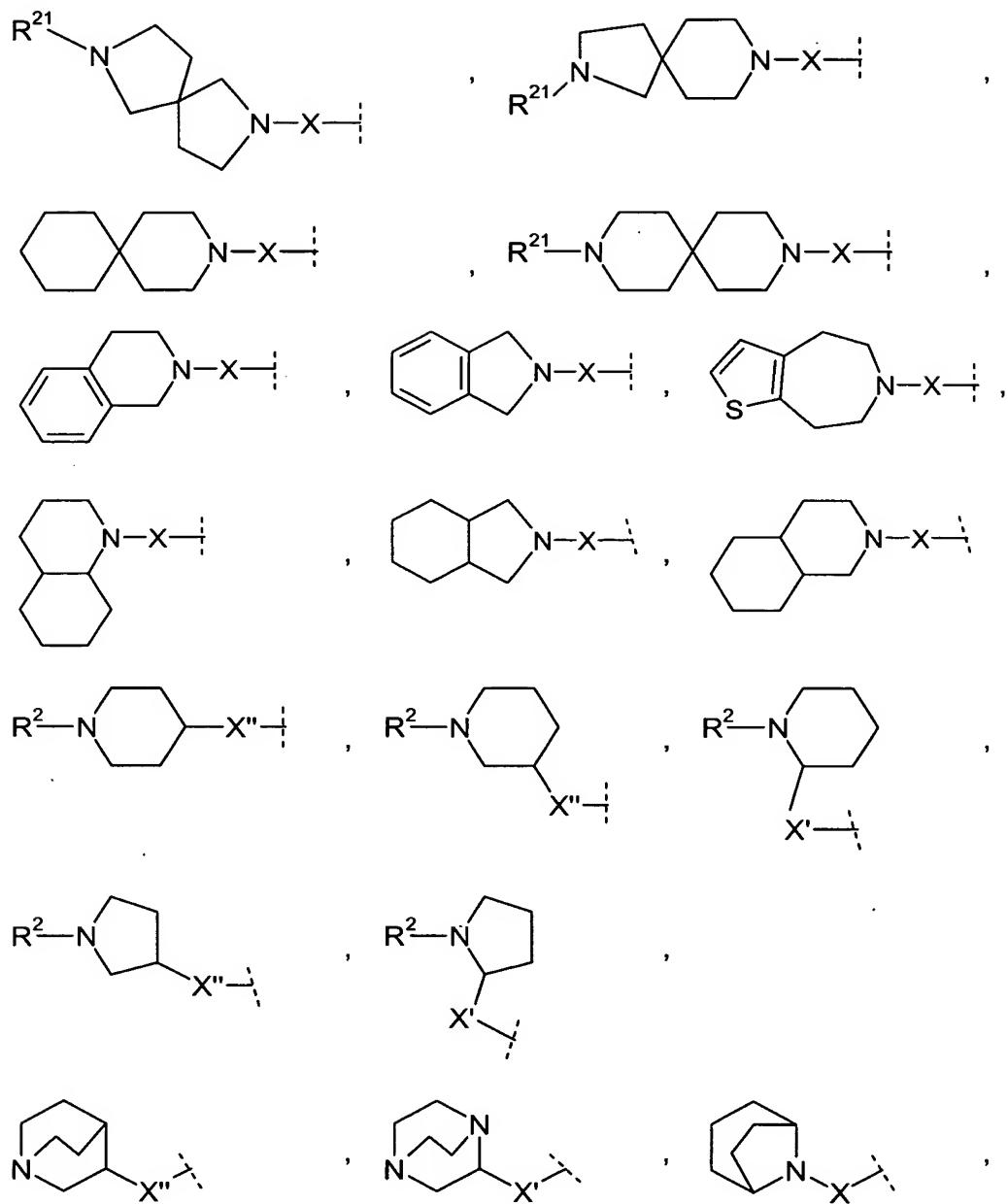


is defined according to one of the following partial formulae

10







wherein one or more H atoms of the heterocycle formed by the group R^1R^2N- may be replaced by R^{14} and the ring attached to the heterocycle formed by the group R^1R^2N- may be mono- or polysubstituted by R^{20} at one or more C atoms, and in

the case of a phenyl ring it may also additionally be monosubstituted by nitro and

X', X" independently of one another denote a single bond or C₁₋₃-alkylene and

5 if the group Y is linked to X' or X" via a C atom, may also denote -C₁₋₃-alkylene-O-, -C₁₋₃-alkylene-NH- or -C₁₋₃-alkylene-N(C₁₋₃-alkyl)-, and

10 X" may additionally also denote -O-C₁₋₃-alkylene-, -NH-C₁₋₃-alkylene- or -N(C₁₋₃-alkyl)-C₁₋₃-alkylene- and

15 if the group Y is linked to X" via a C atom, may also denote -NH-, -N(C₁₋₃-alkyl)- or -O-,

20 while in the definitions given hereinbefore for X', X" in each case a C atom may be substituted by R¹⁰, preferably by a hydroxy, ω-hydroxy-C₁₋₃-alkyl, ω-(C₁₋₄-alkoxy)-C₁₋₃-alkyl and/or C₁₋₄-alkoxy group, and/or one or two C atoms in each case may be substituted by one or two identical or different substituents selected from C₁₋₆-alkyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, C₃₋₇-cycloalkyl, C₃₋₇-cycloalkyl-C₁₋₃-alkyl, C₄₋₇-cycloalkenyl and C₄₋₇-cycloalkenyl-C₁₋₃-alkyl, while two alkyl and/or alkenyl substituents may be joined together forming a carbocyclic ring system, and

25 in X', X" independently of one another in each case one or more C atoms may be mono- or polysubstituted by F and/or in each case one or two C atoms independently of one another may be monosubstituted by Cl or Br and

30 wherein R², R¹⁰, R¹³, R¹⁴, R¹⁸, R²⁰, R²¹ and X have the meanings given hereinbefore and hereinafter.

In the preferred and particularly preferred definitions of R^1R^2N listed above the following definitions of the substituent R^{14} are preferred: C_{1-4} -alkyl, C_{2-4} -alkenyl, C_{2-4} -alkynyl, C_{3-7} -cycloalkyl, C_{3-7} -cycloalkyl- C_{1-3} -alkyl, hydroxy, ω -hydroxy- C_{1-3} -alkyl, C_{1-4} -alkoxy, ω -(C_{1-4} -alkoxy)- C_{1-3} -alkyl, C_{1-4} -alkyl-carbonyl, carboxy, C_{1-4} -alkoxy-carbonyl, hydroxy-carbonyl- C_{1-3} -alkyl, C_{1-4} -alkoxycarbonyl- C_{1-3} -alkyl, C_{1-4} -alkoxy-carbonylamino, C_{1-4} -alkoxy-carbonylamino- C_{1-3} -alkyl, amino, C_{1-4} -alkyl-amino, C_{3-7} -cycloalkyl-amino, N -(C_{3-7} -cycloalkyl)- N -(C_{1-4} -alkyl)-amino, di-(C_{1-4} -alkyl)-amino, amino- C_{1-3} -alkyl, C_{1-4} -alkyl-amino- C_{1-3} -alkyl, C_{3-7} -cycloalkyl-amino- C_{1-3} -alkyl, N -(C_{3-7} -cycloalkyl)- N -(C_{1-4} -alkyl)-amino- C_{1-3} -alkyl, di-(C_{1-4} -alkyl)-amino- C_{1-3} -alkyl, cyclo- C_{3-6} -alkyleneimino- C_{1-3} -alkyl, aminocarbonyl, C_{1-4} -alkyl-amino-carbonyl, C_{3-7} -cycloalkyl-amino-carbonyl, N -(C_{3-7} -cycloalkyl)- N -(C_{1-4} -alkyl)-amino-carbonyl, di-(C_{1-4} -alkyl)-amino-carbonyl, pyridinyl-oxy, pyridinyl-amino, pyridinyl- C_{1-3} -alkyl-amino.

Most particularly preferred definitions of the substituent R^{14} are C_{1-4} -alkyl, hydroxy, ω -hydroxy- C_{1-3} -alkyl, C_{1-4} -alkoxy, ω -(C_{1-4} -alkoxy)- C_{1-3} -alkyl, amino- C_{1-3} -alkyl, C_{1-4} -alkyl-amino- C_{1-3} -alkyl, C_{3-7} -cycloalkyl-amino- C_{1-3} -alkyl, N -(C_{3-7} -cycloalkyl)- N -(C_{1-4} -alkyl)-amino- C_{1-3} -alkyl, di-(C_{1-4} -alkyl)-amino- C_{1-3} -alkyl- and cyclo- C_{3-6} -alkyleneimino- C_{1-3} -alkyl.

20 Preferably X denotes a C_{1-6} -alkylene bridge wherein

- a - CH_2 - group not adjacent to the N atom of the R^1R^2N group may be replaced by - $CH=CH$ - or - $C\equiv C$ - and/or
- a - CH_2 - group not adjacent to the N atom of the R^1R^2N group may be replaced by -O-, -S-, -CO- or -NR⁴⁻, particularly preferably by -O-, -S- or -NR⁴⁻, in such a way that in each case two O, S or N atoms or an O and an S atom are not directly joined together,

while R⁴ and Y may be joined together forming a heterocyclic ring system,

30 while the bridge X may be connected to R¹ including the N atom attached to R¹ and X, forming a heterocyclic group, while the bridge X may additionally also be

connected to R² including the N atom attached to R² and X, forming a heterocyclic group, and

two C atoms or a C and an N atom of the alkylene bridge may be joined together
5 by an additional C₁₋₄-alkylene bridge, and

a C atom may be substituted by R¹⁰ and/or one or two C atoms in each case may
be substituted by one or two identical or different substituents selected from C₁₋₆-
alkyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, C₃₋₇-cycloalkyl, C₃₋₇-cycloalkyl-C₁₋₃-alkyl, C₄₋₇-
10 cycloalkenyl and C₄₋₇-cycloalkenyl-C₁₋₃-alkyl, while two alkyl and/or alkenyl
substituents may be joined together, forming a carbocyclic ring system,
particularly a cyclopropyl, cyclobutyl or cyclopentyl group.

Preferably in the group X a -CH₂- group immediately adjacent to the group R¹R²N-
15 is not replaced by -O, -S, -(SO), -(SO₂), -CO or -NR⁴-.

If in the group X a -CH₂- group of the alkylene bridge is replaced according to the
invention, this -CH₂- group is preferably not directly connected to a heteroatom, a
double or triple bond.

20 Preferably the alkylene bridge X, X' or X" has no or not more than one imino
group. The position of the imino group within the alkylene bridge X, X' or X" is
preferably such that no aminal function is formed together with the amino group
NR¹R² or another adjacent amino group or two N atoms are not adjacent to one
25 another.

Preferably X denotes an unbranched C₁₋₄-alkylene bridge and

if the group Y is linked to X via a C atom, it may also denote
30 -CH₂-CH=CH-, -CH₂-C≡C-, C₂₋₄-alkylenoxy or C₂₋₄-alkylene-NR⁴,

while R⁴ and Y may be joined together forming a heterocyclic ring system,

while the bridge X may be connected to R¹ including the N atom attached to R¹ and X, forming a heterocyclic group, and

5

in X a C atom may be substituted by R¹⁰ and/or one or two C atoms in each case may be substituted by one or two identical or different substituents selected from C₁₋₆-alkyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, C₃₋₇-cycloalkyl, C₃₋₇-cycloalkyl-C₁₋₃-alkyl, C₄₋₇-cycloalkenyl and C₄₋₇-cycloalkenyl-C₁₋₃-alkyl-, while two alkyl and/or alkenyl

10 substituents may be joined together, forming a carbocyclic ring system and

in the above-mentioned groups and residues one or more C atoms may be mono- or polysubstituted by F and/or one or two C atoms independently of one another may be monosubstituted by Cl or Br and

15

wherein R¹, R⁴ and R¹⁰ are defined as hereinbefore and hereinafter.

Particularly preferably, X denotes -CH₂-, -CH₂-CH₂-, -CH₂-CH₂-CH₂- or -CH₂-CH₂-NR⁴-CO- and

20

if the group Y is linked to X via a C atom, it also denotes -CH₂-CH=CH-, -CH₂-C≡C-, -CH₂-CH₂-O-, -CH₂-CH₂-CH₂-O- or -CH₂-CH₂-NR⁴- or -CH₂-CH₂-CH₂-NR⁴-,

25

while R⁴ and Y may be joined together, forming a heterocyclic ring system,

while the bridge X may be connected to R¹ including the N atom attached to R¹ and X, forming a heterocyclic group, and

30

in X a C atom may be substituted by R¹⁰, preferably a hydroxy, ω-hydroxy-C₁₋₃-alkyl, ω-(C₁₋₄-alkoxy)-C₁₋₃-alkyl and/or C₁₋₄-alkoxy group, and/or

one or two C atoms independently of one another may each be substituted by one or two identical or different C₁₋₄-alkyl groups, while two alkyl groups may be joined together, forming a carbocyclic ring system , and

- 5 in each case one or more C atoms may be mono- or polysubstituted by F and/or in each case one or two C atoms may independently of one another be monosubstituted by Cl or Br.

Most particularly preferably, if the group Y is linked to X via a C atom, X denotes

- 10 -CH₂-CH₂-O-, which may be substituted as specified hereinbefore.

If R⁴ is linked to Y forming a heterocyclic ring system, Y preferably has the meaning phenyl and R⁴ preferably has the meaning C₂₋₆-alkyl or C₂₋₆-alkenyl.

Preferred heterocyclic ring systems are indole, dihydroindole, dihydroquinoline and

- 15 tetrahydroquinoline.

The group R⁴ preferably only represents vinyl if R⁴ is attached to Y, forming a heterocyclic ring system.

- 20 The group X preferably has no carbonyl group.

Advantageously, the group X with the meaning C₂₋₄-alkyleneoxy, particularly -CH₂-CH₂-O-, has no hydroxy substituents.

- 25 If a C atom is substituted in X, X' or X'', the preferred substituents are selected from among the C₁₋₄-alkyl, C₂₋₄-alkenyl, C₂₋₄-alkynyl, C₃₋₇-cycloalkyl, C₃₋₇-cycloalkyl-C₁₋₃-alkyl, hydroxy, ω-hydroxy-C₁₋₃-alkyl, ω-(C₁₋₄-alkoxy)-C₁₋₃-alkyl- and C₁₋₄-alkoxy groups. Moreover, in X, X' or X'' , a C atom may be disubstituted and/or one or two C atoms may be mono- or disubstituted, while preferred
- 30 substituents are selected from among C₁₋₄-alkyl, C₂₋₄-alkenyl, C₂₋₄-alkynyl, C₃₋₇-cycloalkyl and C₃₋₇-cycloalkyl-C₁₋₃-alkyl, and two C₁₋₄-alkyl and/or C₂₋₄-alkenyl

substituents may also be joined together forming a saturated or monounsaturated carbocyclic ring.

Most particularly preferred substituents for one or two C atoms in X, X' or X" are
5 selected from methyl, ethyl, n-propyl, i-propyl, cyclopropyl, cyclopropylmethyl, while two alkyl substituents on a C atom may also be joined together, forming a carbocyclic ring.

If Y denotes a fused bicyclic ring system, a preferred definition of the group X is
10 -CH₂-, -CH₂-CH₂- and -CH₂-CH₂-CH₂-, particularly -CH₂- or -CH₂-CH₂-, which may be substituted as specified.

If in the group X, X' or X" one or more C atoms is or are substituted by a hydroxy and/or C₁₋₄-alkoxy group, the substituted C atom is preferably not directly adjacent to another heteroatom.
15

Preferably Z is a single bond, -CH₂- or -CH₂-CH₂-, while one or two C atoms independently of one another may be mono- or disubstituted by F, CH₃ or CF₃ and/or monosubstituted by Cl.

20 Particularly preferred definitions of the group Z are a single bond, -CH₂- or -CH₂-CH₂-, particularly a single bond.

According to a first embodiment the compounds according to the invention have a
25 bridge W, which is selected from the group -CR^{6a}R^{6b}-O-, -CR^{6a}R^{6b}-NR⁸-, -CR^{7a}R^{7b}-CR^{7c}R^{7d}- and -NR⁸-CR^{6a}R^{6b}-.

According to a second embodiment the compounds according to the invention have a bridge W, which denotes -CR^{7a}=CR^{7c}-.

30

W preferably denotes -CH₂-O-, -CH₂-NR⁸-, -CH₂-CH₂- or -CH=CH-, while in the last two meanings in each case one or two C atoms may be substituted independently of one another by F, Cl, CH₃ or CF₃. In the above definitions -CH₂-O- and -CH₂-NR⁸- the group A is advantageously attached to the bridge W via a C atom.

5

Preferred definitions of the substituent R⁸ are H and methyl.

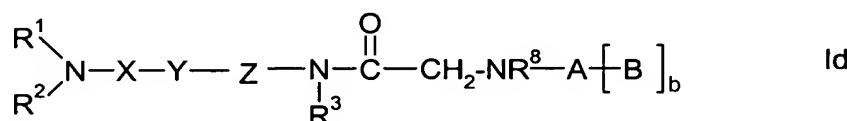
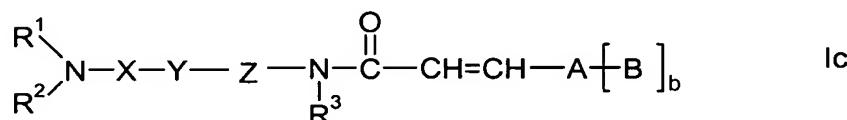
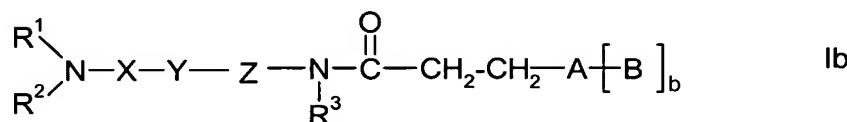
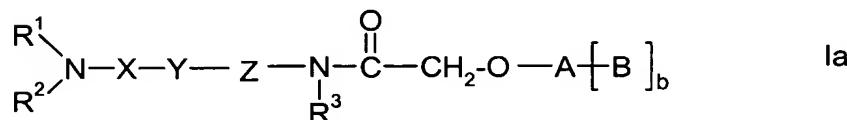
Particularly preferred definitions of the group W are -CH₂-O-, -CH₂-NH-, -CH₂-NCH₃- and -CH₂-CH₂, particularly -CH₂-O-.

10

If the group W has the above meaning of an optionally substituted -CH=CH- bridge, the group Z is preferably a single bond.

15

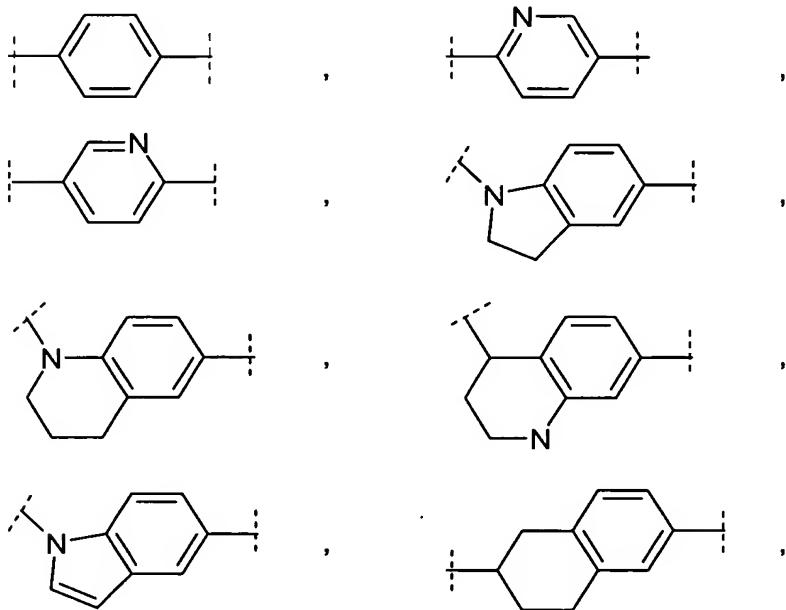
Preferred embodiments of this invention therefore comprise compounds which may each be described by the following formulae Ia, Ib, Ic and Id:



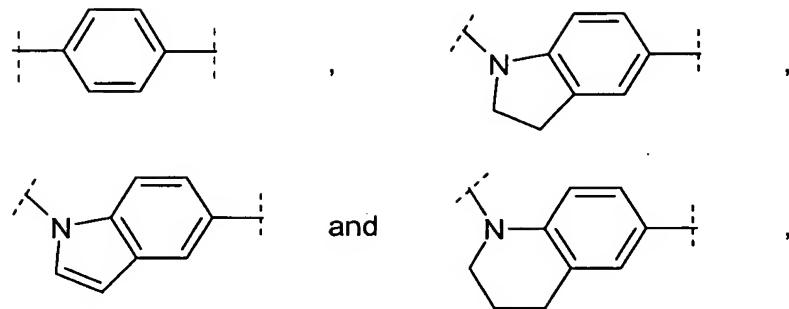
wherein R¹, R², X, Y, Z, R³, R⁸, A, B and b are defined as hereinbefore and hereinafter, particularly have the meanings given as being preferred, while R⁸ preferably denotes H or methyl.

- 5 The group Y preferably has a meanings selected from among the bivalent cyclic groups phenyl, pyridinyl, naphthyl, tetrahydronaphthyl, indolyl, dihydroindolyl, quinolinyl, dihydroquinolinyl, tetrahydroquinolinyl, isoquinolinyl, dihydroisoquinolinyl or tetrahydro-isoquinolinyl, while the above-mentioned cyclic groups may be mono- or polysubstituted by R²⁰ at one or more C atoms and in
- 10 the case of a phenyl group may also additionally be monosubstituted by nitro, and/or by R²¹ at one or more N atoms. R¹ may be attached to Y and/or X may be attached to Y as specified hereinbefore.

particularly preferably, one definition of the group Y is selected from the following
 15 bivalent cyclic groups



and particularly Y has one of the following definitions:



while the cyclic groups listed above may be mono- or polysubstituted by R²⁰ at
 5 one or more C atoms, and in the case of a phenyl group may also additionally be monosubstituted by nitro, and/or one or more NH groups may be substituted by R²¹.

The group Y is preferably unsubstituted or mono- or disubstituted.

10

Particularly preferred substituents R²⁰ of the group Y are selected from among fluorine, chlorine, bromine, cyano, nitro, C₁₋₄-alkyl, C₂₋₆-alkenyl, hydroxy, ω-hydroxy-C₁₋₃-alkyl, C₁₋₄-alkoxy, trifluoromethyl, trifluoromethoxy, C₂₋₄-alkynyl, C₁₋₄-alkoxycarbonyl, ω-(C₁₋₄-alkoxy)-C₁₋₃-alkyl, C₁₋₄-alkoxy-carbonylamino, amino, C₁₋₄-alkyl-amino, di-(C₁₋₄-alkyl)-amino, aminocarbonyl, C₁₋₄-alkyl-amino-carbonyl, di-(C₁₋₄-alkyl)-amino-carbonyl, -CH=N-OH and -CH=N-O-C₁₋₄-alkyl.

15

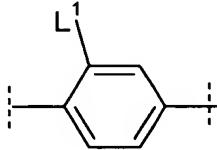
Most particularly preferred substituents R²⁰ of the group Y are selected from among fluorine, chlorine, bromine, cyano, C₁₋₃-alkyl, C₁₋₃-alkoxy, trifluoromethyl, trifluoromethoxy, and, in the case of a phenyl ring, nitro as well.

20

If Y is a phenyl or pyridinyl group, the phenyl or pyridinyl group is at least monosubstituted, particularly if the group W denotes optionally substituted -CH=CH- or -CH₂-CH₂-.

Most particularly preferably, the group Y denotes substituted phenylene of the

partial
formula



, wherein L¹ has one of the meanings given hereinbefore for R²⁰,

preferably F, Cl, Br, I, CH₃, CF₃, OCH₃, OCF₃, CN or NO₂, or denotes H.

5

The group Y preferably denotes monosubstituted phenylene according to the above partial formula, if the bridge W denotes -CH=CH-.

A preferred meaning of the group A is aryl or heteroaryl.

10

Preferably the group A is selected from among the cyclic groups phenyl, pyridinyl or naphthyl, which may be mono- or polysubstituted by R²⁰ at one or more C atoms, in the case of a phenyl ring may also additionally be monosubstituted by nitro.

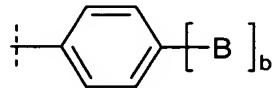
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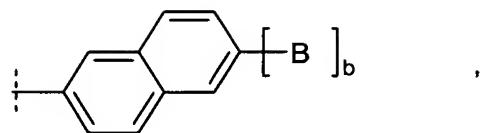
If b has the value 0, the group A is preferably mono-, di or trisubstituted.

If b has the value 1, the group A is preferably unsubstituted or mono- or disubstituted.

20

Most particularly preferably, A is one of the following groups





while the groups listed may be mono- or polysubstituted by R^{20} as specified. The definitions phenyl and pyridyl given for the group A are preferred when b has the value 1.

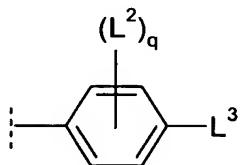
5

Particularly preferred substituents R^{20} for the group A are selected from among fluorine, chlorine, bromine, cyano, C_{1-4} -alkyl, C_{2-6} -alkenyl, -CHO, hydroxy, ω -hydroxy- C_{1-3} -alkyl, C_{1-4} -alkoxy, trifluoromethyl, trifluoromethoxy, C_{2-4} -alkynyl, carboxy, C_{1-4} -alkoxycarbonyl, ω -(C_{1-4} -alkoxy)- C_{1-3} -alkyl, C_{1-4} -alkoxy-

10 carbonylamino, amino, C_{1-4} -alkyl-amino, di-(C_{1-4} -alkyl)-amino, cyclo- C_{3-6} -alkyleneimino, aminocarbonyl, C_{1-4} -alkyl-amino-carbonyl, di-(C_{1-4} -alkyl)-amino-carbonyl, - $CH=N-OH$ and - $CH=N-O-C_{1-4}$ -alkyl.

15 Most particularly preferred substituents R^{20} for the group A are selected from among fluorine, chlorine, bromine, cyano, C_{1-4} -alkyl, C_{1-4} -alkoxy, trifluoromethyl, trifluoromethoxy, carboxy, C_{1-4} -alkoxycarbonyl, C_{1-4} -alkyl-amino, di-(C_{1-4} -alkyl)-amino,

20 If b has the value 0, a particularly preferred meaning of the group A is substituted phenyl of the partial formula



wherein

5 L^2 has one of the meanings given for R^{20} or denotes H, preferably F, Cl,
 Br, I, CH_3 , CF_3 , OCH_3 , OCF_3 , CN or NO_2 ,

10 L^3 has one of the meanings given for R^{20} or denotes H, preferably F, Cl,
 Br, I, CF_3 , OCF_3 , CN, NO_2 , C_{1-4} -alkyl, C_{3-7} -cycloalkyl, C_{3-7} -cycloalkyl- C_{1-3} -alkyl, C_{1-4} -alkoxy, C_{3-7} -cycloalkyl-O, C_{3-7} -cycloalkyl- C_{1-3} -alkoxy, -COO- C_{1-4} -alkyl or -COOH,

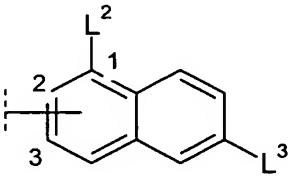
15 q has the value 0, 1 or 2,

20 with the proviso that the phenyl and naphthyl group may be at most only monosubstituted by nitro.

Particularly preferably, A is substituted phenyl according to the above partial formula in which q denotes 1 or 2 and/or at least one substituent L^2 is in the meta position to the substituent L^3 .

The group A preferably denotes substituted phenyl according to the above partial formula, while q has the value 1 or 2 if the bridge W represents - $CH=CH$, the group Y denotes phenyl and b has the value 0.

25 Another preferred partial formula for A, particularly if b has the value 0, is



, wherein the bond to the group W is made via the C atom with position number 2 or 3.

If b has the value 1, a preferred meaning for the group B is aryl or heteroaryl, which may be substituted as specified.

5 Preferred definitions of the group B are selected from among phenyl, pyridyl, thieryl and furanyl. Particularly preferably, the group B denotes phenyl. The group B with the meanings given above may be mono- or polysubstituted by R²⁰, and a phenyl group may additionally also be monosubstituted by nitro. Preferably the group B is mono-, di- or trisubstituted, particularly mono- or disubstituted. In the
10 event of a monosubstitution the substituent is preferably in the para position to the group A.

Particularly preferred substituents R²⁰ for the group B are selected from among fluorine, chlorine, bromine, cyano, nitro, C₁₋₄-alkyl, hydroxy, ω-hydroxy-C₁₋₃-alkyl,
15 C₁₋₄-alkoxy, trifluoromethyl, trifluoromethoxy, C₂₋₄-alkynyl, carboxy, C₁₋₄-alkoxy-carbonyl, ω-(C₁₋₄-alkoxy)-C₁₋₃-alkyl, C₁₋₄-alkoxy-carbonylamino, amino, C₁₋₄-alkyl-amino, di-(C₁₋₄-alkyl)-amino, cyclo-C₃₋₆-alkyleneimino, aminocarbonyl, C₁₋₄-alkyl-amino-carbonyl- and di-(C₁₋₄-alkyl)-amino-carbonyl.
20 Most particularly preferred substituents R²⁰ for the group B are selected from among fluorine, chlorine, bromine, cyano, CF₃, C₁₋₃-alkyl, C₁₋₄-alkoxy and trifluoromethoxy.

The group B preferably denotes an at least monosubstituted phenyl ring, if the
25 bridge W denotes -CH=CH-, the group Y denotes phenyl and b has the value 1.

R⁴ has one of the meanings given for R¹⁷, preferably one of the meanings given for R¹⁶.

Particularly preferred meanings of the substituent R⁴ are H, C₁₋₆-alkyl and C₃₋₆-alkenyl. If R⁴ is attached to Y, forming a heterocyclic ring system, particularly preferred meanings for R⁴ are C₂₋₆-alkyl and C₂₋₆-alkenyl.

5 The groups R^{6a}, R^{6b} represent H, C₁₋₄-alkyl or CF₃, preferably H or methyl, particularly H.

The groups R^{7a}, R^{7b}, R^{7c}, R^{7d} represent H, F, C₁₋₄-alkyl or CF₃, preferably H or methyl, particularly H.

10

The group R⁸ preferably denotes H or methyl.

If R¹¹ is a C₂₋₆-alkenyl or C₂₋₆-alkynyl group, the definitions -CH=CH₂, -CH=CH(CH₃), -CH=C(CH₃)₂ and -C≡CH, -C≡C-CH₃ are preferred.

15

The substituent R²⁰ preferably has none of the following structural elements:

- a) -CO-aryl or -CO-heteroaryl, particularly -CO-phenyl, wherein heteroaryl, aryl and phenyl may be substituted,
- b) -C(=NH)-NH-, wherein the H atoms may be substituted and/or
- c) -NH-CO-NH-, wherein the H atoms may be substituted.

Preferred definitions of the group R²⁰ are halogen, hydroxy, cyano, C₁₋₄-alkyl, C₃₋₇-cycloalkyl and C₁₋₄-alkoxy. Particularly preferably R²⁰ denotes F, Cl, Br, I, OH, cyano, methyl, difluoromethyl, trifluoromethyl, ethyl, n-propyl, iso-propyl, methoxy, difluoromethoxy, trifluoromethoxy, ethoxy, n-propoxy or iso-propoxy.

Preferred definitions of the group R²¹ are C₁₋₄-alkyl, C₁₋₄-alkylcarbonyl, C₁₋₄-alkylsulphonyl, -SO₂-NH₂, -SO₂-NH-C₁₋₃-alkyl, -SO₂-N(C₁₋₃-alkyl)₂ and cyclo-C₃₋₆-alkyleneimino-sulphonyl.

25

30

Cy preferably denotes a C₃₋₇-cycloalkyl, particularly a C₅₋₇-cycloalkyl group, a C₅₋₇-cycloalkenyl group, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl,

thiomorpholinyl, aryl or heteroaryl, while aryl or heteroaryl preferably denotes a monocyclic or fused bicyclic ring system, and the above-mentioned cyclic groups

.5 may be mono- or polysubstituted by R²⁰ at one or more C atoms, and in the case of a phenyl group may also additionally be monosubstituted by nitro, and/or one or more NH groups may be substituted by R²¹.

Preferred compounds according to the invention are those wherein one or more of

10 the groups, residues, substituents and/or indices have one of the meanings given as being preferred.

Particularly preferred compounds according to the invention are those wherein

15 Y denotes phenyl, 1H-indolyl, 2,3-dihydro-1H-indolyl or 1,2,3,4-tetrahydroquinoline according to the definition described above as being preferred, particularly with phenyl substituted by L¹ according to the partial formula given hereinbefore and/or

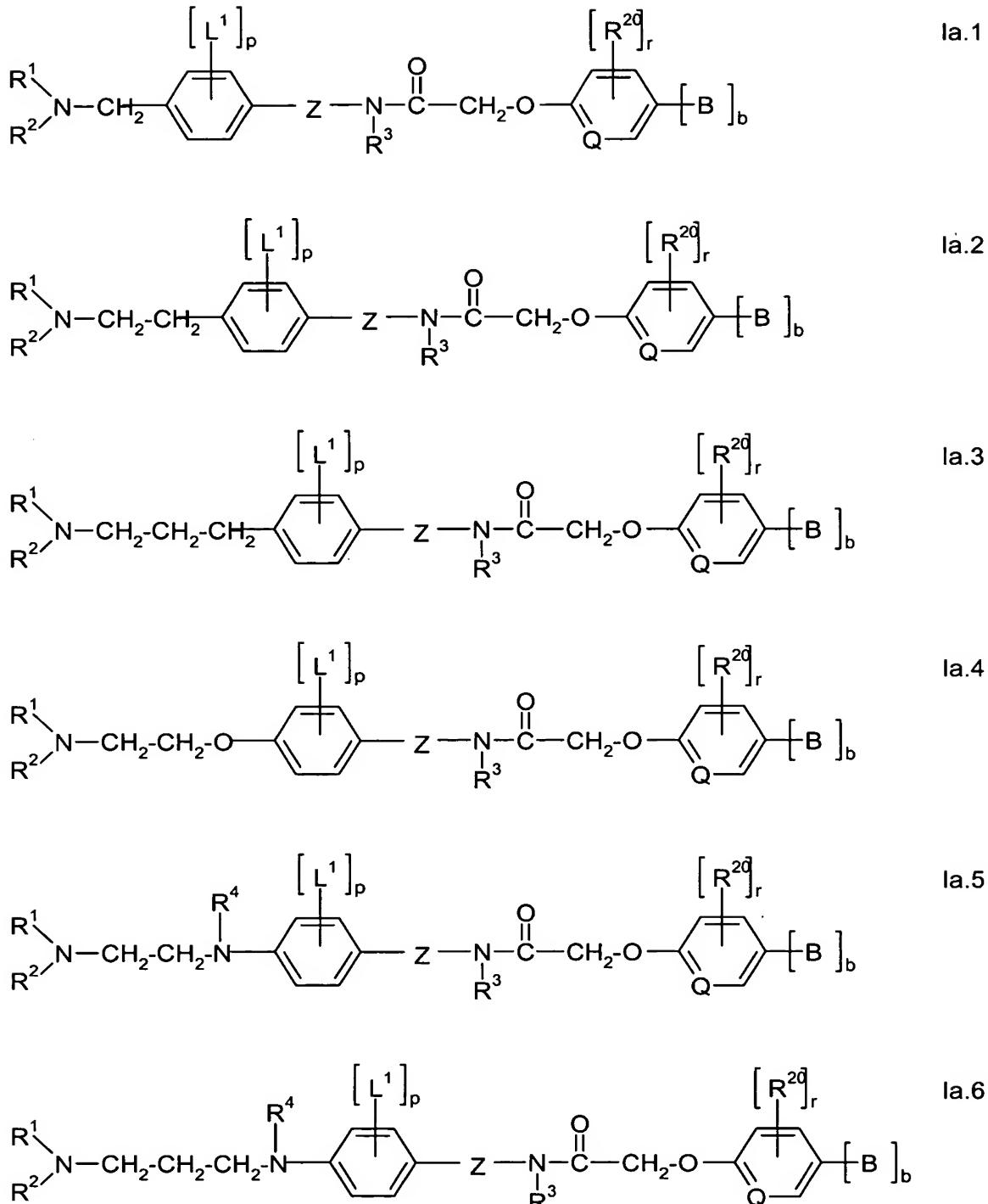
20 A denotes phenyl substituted by L² and L³ according to the partial formula given hereinbefore.

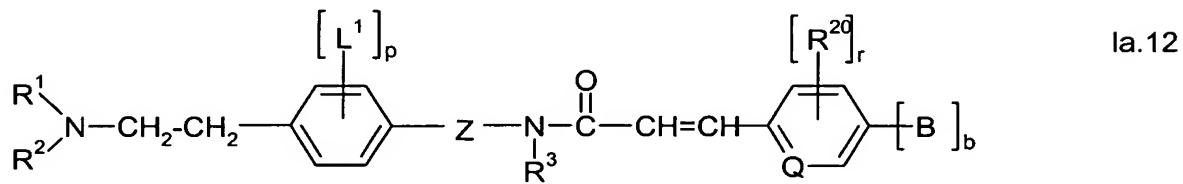
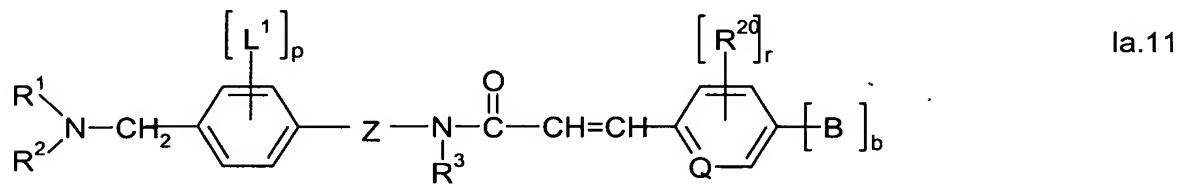
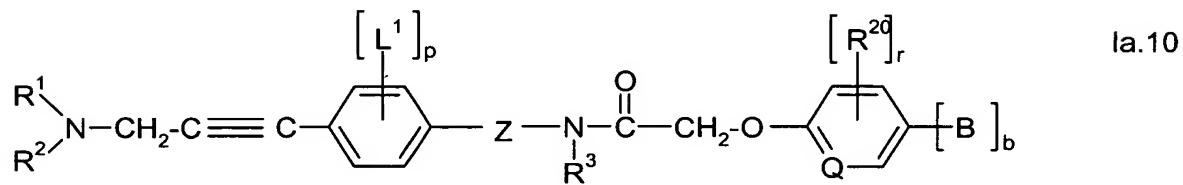
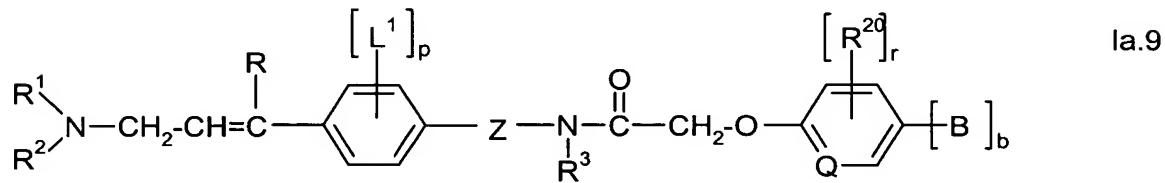
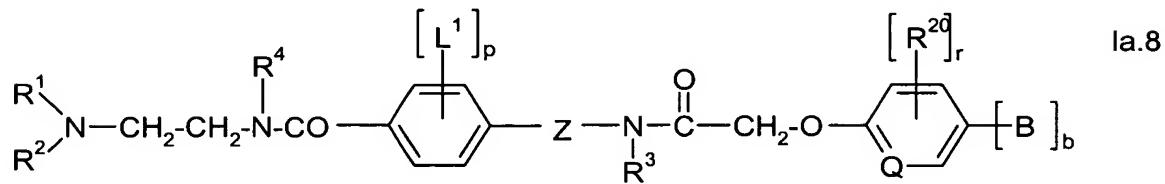
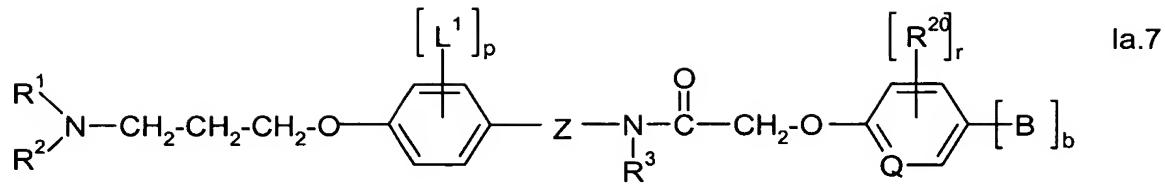
Most particularly preferred compounds according to the invention are those

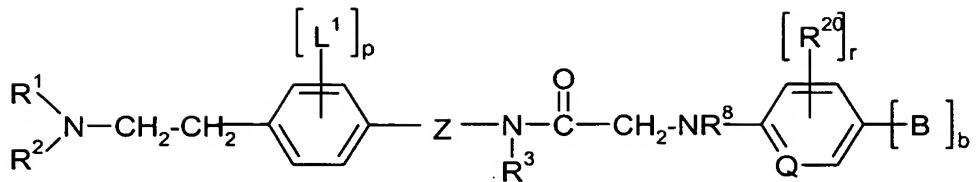
wherein A, X, Y, Z, R¹, R², R³ and W independently of one another have one or

25 more of the above-mentioned preferred meanings.

Preferred groups of compounds according to this invention can be described by the following formulae







wherein R^1 , R^2 , Z , R^3 , R^4 , R^8 , R^{20} , B and b have the meanings given hereinbefore and

- 5 Z preferably denotes a single bond or $-CH_2-CH_2-$,
- 10 R^3 preferably denotes H or methyl,
- 15 R^4 preferably denotes H, C_{1-6} -alkyl or C_{2-6} -alkenyl, while R^4 may be attached to Y forming a heterocyclic ring system, particularly preferably forming an indole, dihydroindole, dihydroquinoline or tetrahydroquinoline group,
- 20 Q denotes CH or N, while CH may be substituted by R^{20} ,
- 25 B preferably denotes aryl or heteroaryl, particularly preferably denotes phenyl, pyridyl, furanyl or thieryl, while B may be mono- or polysubstituted by R^{20} ,
- 30 L^1 preferably denotes fluorine, chlorine, bromine, cyano, nitro, C_{1-3} -alkyl, C_{1-3} -alkoxy, trifluoromethyl, trifluoromethoxy or nitro,
- 35 p has the value 0 or 1,
- 40 R^{20} preferably denotes fluorine, chlorine, bromine, cyano, C_{1-4} -alkyl, C_{2-6} -alkenyl, $-CHO$, hydroxy, ω -hydroxy- C_{1-3} -alkyl, C_{1-4} -alkoxy, trifluoromethyl, trifluoromethoxy, C_{2-4} -alkynyl, carboxy, C_{1-4} -alkoxycarbonyl, ω -(C_{1-4} -alkoxy)alkyl, ω -alkyl, ω -alkenyl, ω -alkynyl, ω -alkoxy, ω -alkenyl, ω -alkynyl, ω -alkoxycarbonyl, ω -alkylcarboxy, ω -alkenylcarboxy, ω -alkynylcarboxy, ω -alkoxyalkyl, ω -alkenylalkyl, ω -alkynylalkyl, ω -alkoxyalkenyl, ω -alkenylalkenyl, ω -alkynylalkenyl, ω -alkoxyalkynyl, ω -alkenylalkynyl, ω -alkynylalkynyl, ω -alkoxyalkoxy, ω -alkenylalkoxy, ω -alkynylalkoxy, ω -alkoxyalkoxyalkyl, ω -alkenylalkoxyalkyl, ω -alkynylalkoxyalkyl, ω -alkoxyalkoxyalkenyl, ω -alkenylalkoxyalkenyl, ω -alkynylalkoxyalkenyl, ω -alkoxyalkoxyalkynyl, ω -alkenylalkoxyalkynyl, ω -alkynylalkoxyalkynyl.

$_{4\text{-alkoxy}}\text{-C}_{1\text{-3}}\text{-alkyl}$, $\text{C}_{1\text{-4}}$ -alkoxy-carbonylamino, amino, $\text{C}_{1\text{-4}}$ -alkyl-amino, di-($\text{C}_{1\text{-4}}$ -alkyl)-amino, cyclo- $\text{C}_{3\text{-6}}$ -alkyleneimino, aminocarbonyl, $\text{C}_{1\text{-4}}$ -alkyl-amino-carbonyl, di-($\text{C}_{1\text{-4}}$ -alkyl)-amino-carbonyl, $-\text{CH}=\text{N-OH}$ and $-\text{CH}=\text{N-O-C}_{1\text{-4}}$ -alkyl,

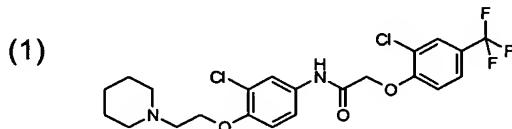
5

r has the value 1, 2 or 3 and, if b has the value 1, r may also denote 0 and

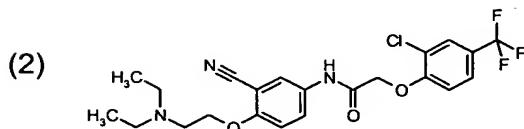
the compounds according to provisos (M1), (M2) and (M3) are not included.

10

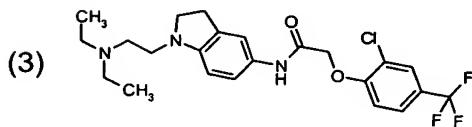
The following individual compounds are particularly preferred:



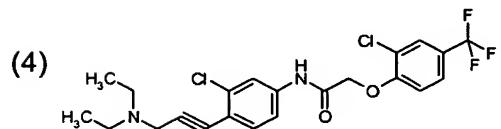
N-[3-chloro-4-(2-piperidin-1-yl-ethoxy)-phenyl]-2-(2-chloro-4-trifluoromethyl-phenoxy)-acetamide



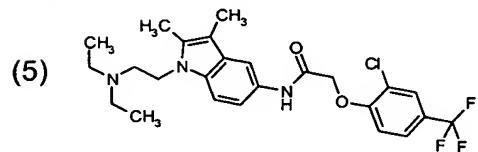
2-(2-chloro-4-trifluoromethyl-phenoxy)-N-[3-cyano-4-(2-diethylaminoethoxy)-phenyl]-acetamide



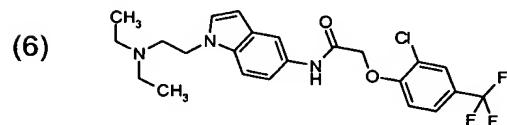
2-(2-chloro-4-trifluoromethyl-phenoxy)-N-[1-(2-diethylamino-ethyl)-2,3-dihydro-1H-indol-5-yl]-acetamide



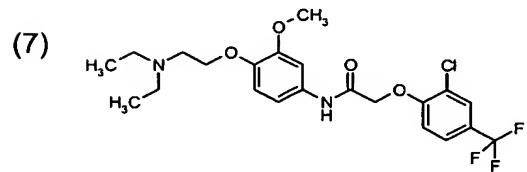
N-[3-chloro-4-(3-diethylamino-prop-1-ynyl)-phenyl]-2-(2-chloro-4-trifluoromethyl-phenoxy)-acetamide



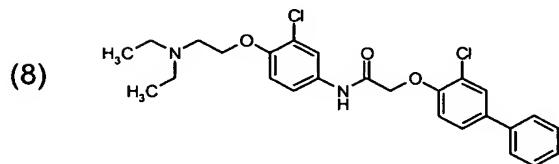
2-(2-chloro-4-trifluoromethyl-phenoxy)-N-[1-(2-diethylamino-ethyl)-2,3-dimethyl-1H-indol-5-yl]-acetamide



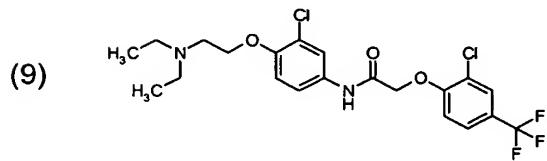
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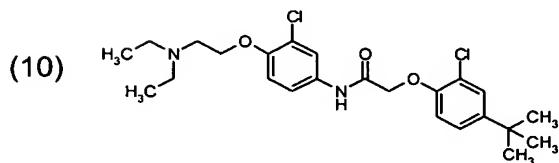
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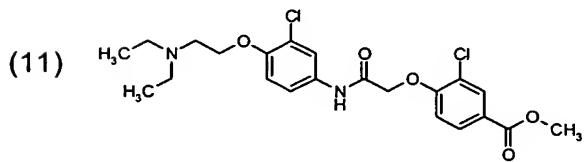
2-(3-chloro-biphenyl-4-yloxy)-N-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-acetamide



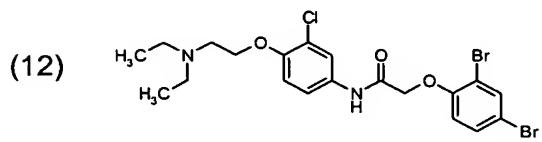
N-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-2-(2-chloro-4-trifluoromethyl-phenoxy)-acetamide



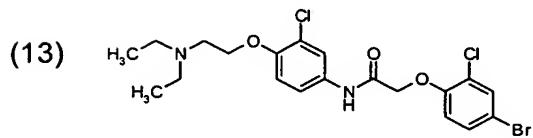
2-(4-tert.-butyl-2-chloro-phenoxy)-N-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-acetamide



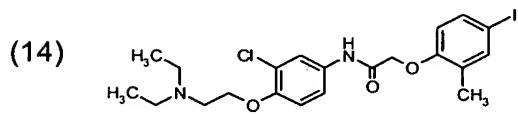
methyl 3-chloro-4-[(3-chloro-4-(2-diethylamino-ethoxy)-phenylcarbamoyl]-methoxy]-benzoate



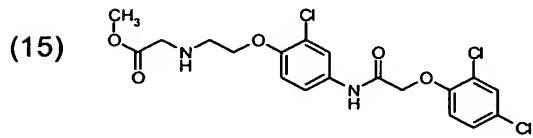
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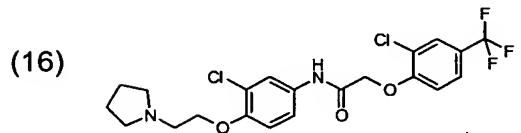
2-(4-bromo-2-chloro-phenoxy)-N-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-acetamide



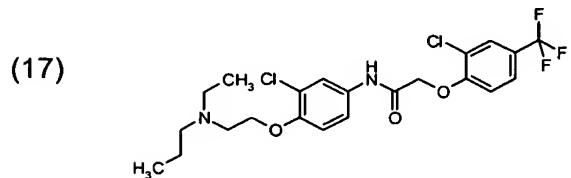
N-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-2-(4-iodo-2-methyl-phenoxy)-acetamide



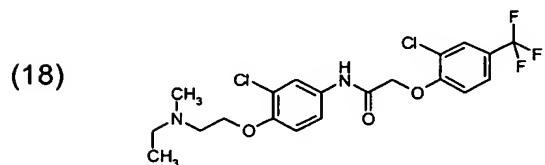
methyl (2-{2-chloro-4-[2-(2,4-dichloro-phenoxy)-acetylamino]-phenoxy}-ethylamino)-acetate



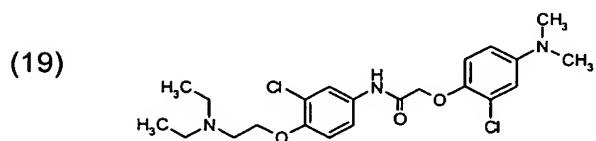
N-[3-chloro-4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-2-(2-chloro-4-trifluoromethyl-phenoxy)-acetamide



N-[3-chloro-4-[2-(ethyl-propyl-amino)-ethoxy]-phenyl]-2-(2-chloro-4-trifluoromethyl-phenoxy)-acetamide

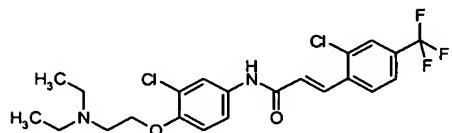


N-[3-chloro-4-[2-(ethyl-methyl-amino)-ethoxy]-phenyl]-2-(2-chloro-4-trifluoromethyl-phenoxy)-acetamide



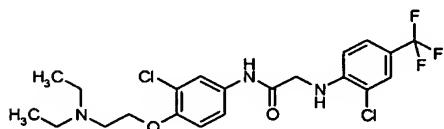
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(20)



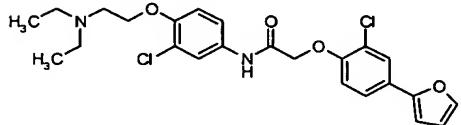
(E)-N-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-3-(2-chloro-4-trifluoromethyl-phenyl)-acrylamide

(21)



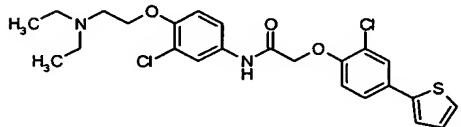
N-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-2-(2-chloro-4-trifluoromethyl-phenylamino)-acetamide

(22)

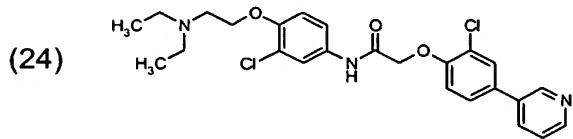


N-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-2-(2-chloro-4-furan-2-yl-phenoxy)-acetamide

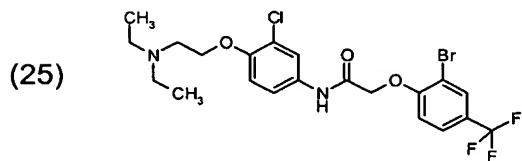
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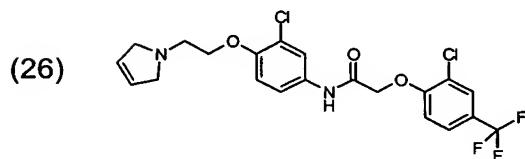
N-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-2-(2-chloro-4-thiophen-2-yl-phenoxy)-acetamide



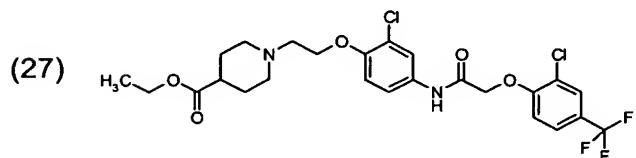
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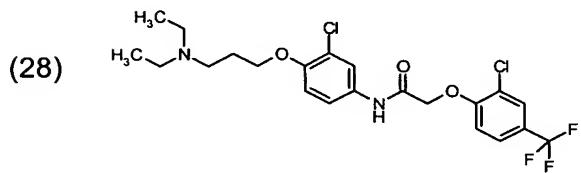
2-(2-bromo-4-trifluoromethyl-phenoxy)-N-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-acetamide



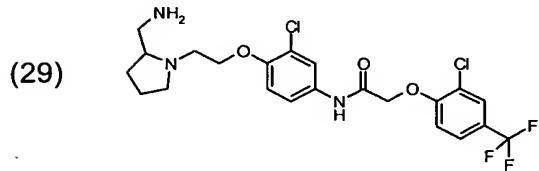
N-[3-chloro-4-[2-(2,5-dihydro-pyrrol-1-yl)-ethoxy]-phenyl]-2-(2-chloro-4-trifluoromethyl-phenoxy)-acetamide



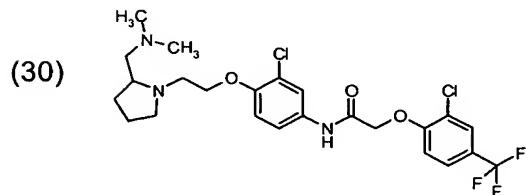
ethyl 1-(2-{2-chloro-4-[2-(2-chloro-4-trifluoromethyl-phenoxy)-acetyl-amino]-phenoxy}-ethyl)-piperidine-4-carboxylate



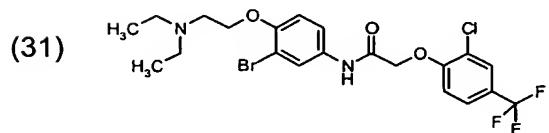
N-[3-chloro-4-(3-diethylamino-propoxy)-phenyl]-2-(2-chloro-4-trifluoromethyl-phenoxy)-acetamide



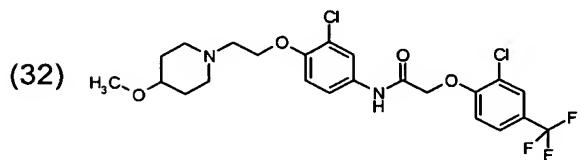
N-[4-{2-(2-aminomethyl-pyrrolidin-1-yl)-ethoxy}-3-chloro-phenyl]-2-(2-chloro-4-trifluoromethyl-phenoxy)-acetamide



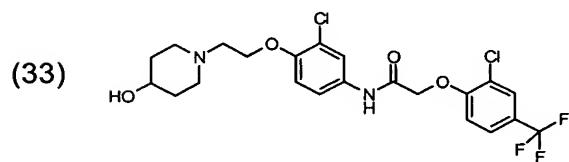
N-[3-chloro-4-{2-(2-dimethylaminomethyl-pyrrolidin-1-yl)-ethoxy}-phenyl]-2-(2-chloro-4-trifluoromethyl-phenoxy)-acetamide



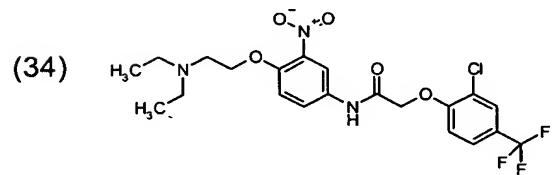
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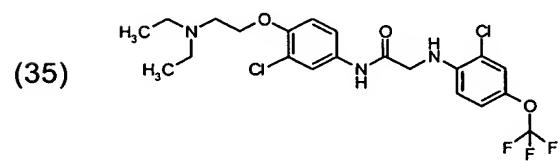
N-{3-chloro-4-[2-(4-methoxy-piperidin-1-yl)-ethoxy]-phenyl}-2-(2-chloro-4-trifluoromethyl-phenoxy)-acetamide



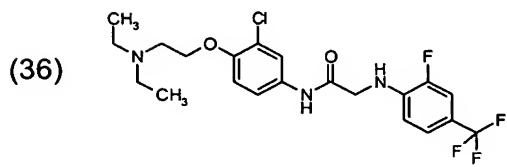
N-{3-chloro-4-[2-(4-hydroxy-piperidin-1-yl)-ethoxy]-phenyl}-2-(2-chloro-4-trifluoromethyl-phenoxy)-acetamide



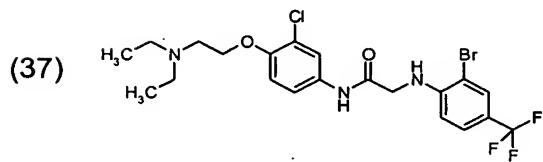
2-(2-chloro-4-trifluoromethyl-phenoxy)-N-[4-(2-diethylamino-ethoxy)-3-nitro-phenyl]-acetamide



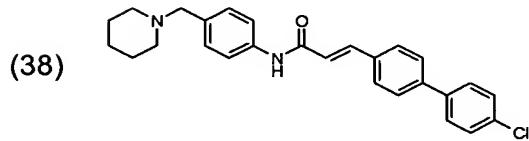
N-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-2-(2-chloro-4-trifluoromethoxy-phenylamino)-acetamide



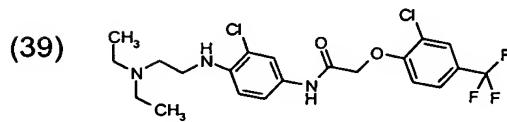
N-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-2-(2-fluoro-4-trifluoromethyl-phenylamino)-acetamide



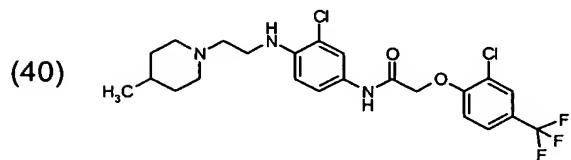
2-(2-bromo-4-trifluoromethyl-phenylamino)-N-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-acetamide



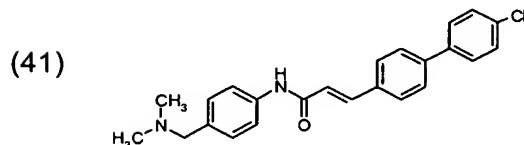
(E)-3-(4'-chloro-biphenyl-4-yl)-N-(4-piperidin-1-ylmethyl-phenyl)-acrylamide



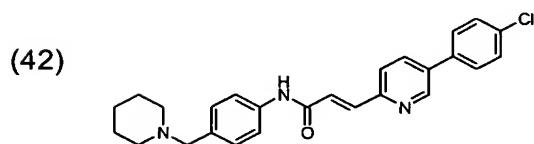
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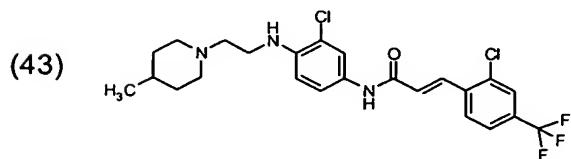
N-[3-chloro-4-[2-(4-methyl-piperidin-1-yl)-ethylamino]-phenyl]-2-(2-chloro-4-trifluoromethyl-phenoxy)-acetamide



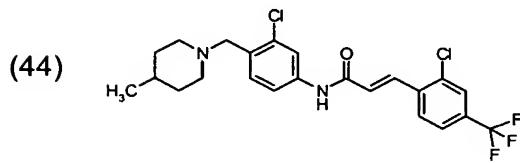
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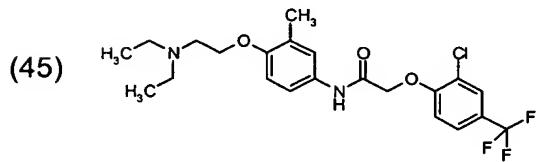
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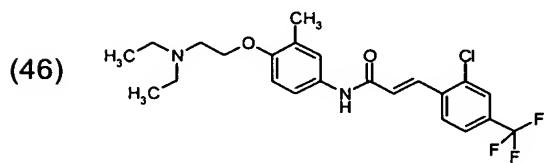
(E)-N-(3-chloro-4-[2-(4-methyl-piperidin-1-yl)-ethylamino]-phenyl)-3-(2-chloro-4-trifluoromethyl-phenyl)-acrylamide



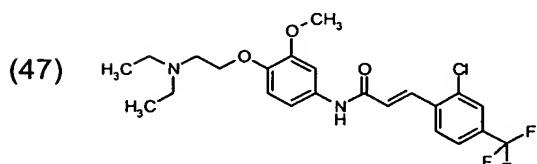
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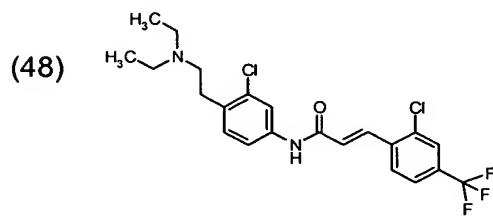
2-(2-chloro-4-trifluoromethyl-phenoxy)-N-[4-(2-diethylamino-ethoxy)-3-methyl-phenyl]-acetamide



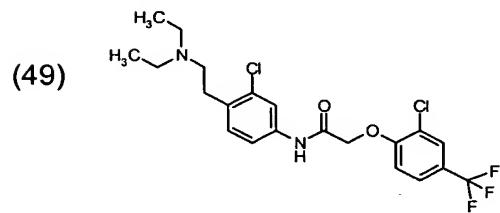
(E)-3-(2-chloro-4-trifluoromethyl-phenyl)-N-[4-(2-diethylamino-ethoxy)-3-methyl-phenyl]-acrylamide



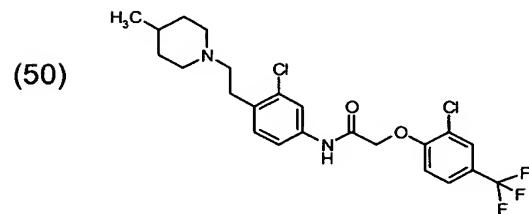
(E)-3-(2-chloro-4-trifluoromethyl-phenyl)-N-[4-(2-diethylamino-ethoxy)-3-methoxy-phenyl]-acrylamide



(E)-N-[3-chloro-4-(2-diethylamino-ethyl)-phenyl]-3-(2-chloro-4-trifluoromethyl-phenyl)-acrylamide



N-[3-chloro-4-(2-diethylamino-ethyl)-phenyl]-2-(2-chloro-4-trifluoromethyl-phenoxy)-acetamide



N-[3-chloro-4-[2-(4-methyl-piperidin-1-yl)-ethyl]-phenyl]-2-(2-chloro-4-trifluoromethyl-phenoxy)-acetamide

including the salts thereof.

Some expressions used hereinbefore and below to describe the compounds according to the invention will now be defined more fully.

5 The term halogen denotes an atom selected from among F, Cl, Br and I, particularly F, Cl and Br.

The term C_{1-n} -alkyl, where n has a value of 3 to 8, denotes a saturated, branched or unbranched hydrocarbon group with 1 to n C atoms. Examples of such groups

10 include methyl, ethyl, n-propyl, iso-propyl, butyl, iso-butyl, sec-butyl, tert-butyl, n-pentyl, iso-pentyl, neo-pentyl, tert-pentyl, n-hexyl, iso-hexyl, etc.

The term C_{1-n} -alkylene, where n may have a value of 1 to 8, denotes a saturated, branched or unbranched hydrocarbon bridge with 1 to n C atoms. Examples of

15 such groups include methylene (- CH_2 -), ethylene (- CH_2-CH_2 -), 1-methyl-ethylene (- $CH(CH_3)-CH_2$ -), 1,1-dimethyl-ethylene (- $C(CH_3)_2-CH_2$ -), n-prop-1,3-ylene (- $CH_2-CH_2-CH_2$ -), 1-methylprop-1,3-ylene (- $CH(CH_3)-CH_2-CH_2$ -), 2-methylprop-1,3-ylene (- $CH_2-CH(CH_3)-CH_2$ -), etc., as well as the corresponding mirror-symmetrical forms.

20

The term C_{2-n} -alkenyl, where n has a value of 3 to 6, denotes a branched or unbranched hydrocarbon group with 2 to n C atoms and at least one C=C-double bond. Examples of such groups include vinyl, 1-propenyl, 2-propenyl, iso-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methyl-1-propenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 3-methyl-2-butenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl etc.

The term C_{2-n} -alkynyl, where n has a value of 3 to 6, denotes a branched or unbranched hydrocarbon group with 2 to n C atoms and a C≡C triple bond.

30 Examples of such groups include ethynyl, 1-propynyl, 2-propynyl, iso-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 2-methyl-1-propynyl; 1-pentynyl, 2-pentynyl, 3-

pentynyl, 4-pentynyl, 3-methyl-2-butynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl etc.

The term C_{1-n} -alkoxy denotes a C_{1-n} -alkyl-O- group, wherein C_{1-n} -alkyl is defined
5 as above. Examples of such groups include methoxy, ethoxy, n-propoxy, iso-
propoxy, n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy, n-pentoxyl, iso-pentoxyl,
neo-pentoxyl, tert-pentoxyl, n-hexoxy, iso-hexoxy etc.

The term C_{1-n} -alkylthio denotes a C_{1-n} -alkyl-S- group, wherein C_{1-n} -alkyl is defined
10 as above. Examples of such groups include methylthio, ethylthio, n-propylthio, iso-
propylthio, n-butylthio, iso-butylthio, sec-butylthio, tert-butylthio, n-pentylthio, iso-
pentylthio, neo-pentylthio, tert-pentylthio, n-hexylthio, iso-hexylthio, etc.

The term C_{1-n} -alkylcarbonyl denotes a C_{1-n} -alkyl-C(=O)- group, wherein C_{1-n} -alkyl
15 is defined as above. Examples of such groups include methylcarbonyl,
ethylcarbonyl, n-propylcarbonyl, iso-propylcarbonyl, n-butylcarbonyl, iso-
butylcarbonyl, sec-butylcarbonyl, tert-butylcarbonyl, n-pentylcarbonyl, iso-
pentylcarbonyl, neo-pentylcarbonyl, tert-pentylcarbonyl, n-hexylcarbonyl, iso-
hexylcarbonyl, etc.

20 The term C_{3-n} -cycloalkyl denotes a saturated mono-, bi-, tri- or spirocyclic
group with 3 to n C atoms. Examples of such groups include cyclopropyl,
cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl,
cyclododecyl, bicyclo[3.2.1.]octyl, spiro[4.5]decyl, norpinyl, norbonyl, norcaryl,
25 adamanyl, etc.

The term C_{5-n} -cycloalkenyl denotes a monounsaturated mono-, bi-, tri- or
spirocyclic group with 5 to n C atoms. Examples of such groups include
cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, cyclononenyl, etc.

30

The term C_{3-n} -cycloalkylcarbonyl denotes a C_{3-n} -cycloalkyl-C(=O) group, wherein C_{3-n} -cycloalkyl is defined as above.

5 The term aryl denotes a carbocyclic, aromatic ring system, such as for example phenyl, biphenyl, naphthyl, anthracenyl, phenanthrenyl, fluorenyl, indenyl, pentalenyl, azulenyl, biphenylenyl, etc. A particularly preferred meaning of "aryl" is phenyl.

10 The term cyclo- C_{3-7} -alkyleneimino denotes a 4- to 7-membered ring which has 3 to 7 methylene units as well as an imino group, the bond to the rest of the molecule being made via the imino group.

15 The term cyclo- C_{3-7} -alkyleneimino-carbonyl denotes a cyclo- C_{3-7} -alkyleneimino ring as defined hereinbefore which is linked to a carbonyl group via the imino group.

20 The term heteroaryl used in this application denotes a heterocyclic, aromatic ring system which comprises in addition to at least one C atom one or more heteroatoms selected from N, O and/or S. Examples of such groups are furanyl, thiophenyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, isoxazolyl, isothiazolyl, 1,2,3-triazolyl, 1,3,5-triazolyl, pyranyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,2,3-triazinyl, 1,2,4-triazinyl, 1,3,5-triazinyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, tetrazolyl, thiadiazinyl, indolyl, isoindolyl, benzofuranyl, benzothiophenyl (thianaphthetyl), indazolyl, benzimidazolyl, benzthiazolyl, benzisothiazolyl, benzoxazolyl, benzisoxazolyl, purinyl, quinazolinyl, quinoxazinyl, quinolinyl, isoquinolinyl, quinoxalinyl, naphthyridinyl, pteridinyl, carbazolyl, azepinyl, diazepinyl, acridinyl, etc. The term heteroaryl also comprises the partially hydrogenated heterocyclic, aromatic ring systems, particularly those listed above. Examples of such partially hydrogenated heterocycles are 2,3-dihydrobenzofuranyl, pyrolinyl, pyrazolinyl, indolinyl, oxazolidinyl, oxazolinyl,

oxazepinyl, etc. Particularly preferably, heteroaryl denotes a heteroaromatic mono- or bicyclic ring system.

5 Terms such as aryl-C_{1-n}-alkyl, heteroaryl-C_{1-n}-alkyl, etc. refer to C_{1-n}-alkyl, as defined above, which is substituted with an aryl or heteroaryl group.

Many of the terms given above may be used repeatedly in the definition of a formula or group and in each case have one of the meanings given above, independently of one another.

10

The term "unsaturated", e.g. in "unsaturated carbocyclic group" or "unsaturated heterocyclic group", as used particularly in the definition of the group Cy, comprises, in addition to the mono- or polyunsaturated groups, the corresponding totally unsaturated groups, but particularly the mono- and diunsaturated groups.

15

The term "optionally substituted" used in this application indicates that the group thus designated is either unsubstituted or mono- or polysubstituted by the substituents specified. If the group in question is polysubstituted, the substituents may be identical or different.

20

The H atom of any carboxy group present or an H atom (imino or amino group) bonded to an N atom may in each case be replaced by a group which can be cleaved in vivo. By a group which can be cleaved in vivo from an N atom is meant for example a hydroxy group, an acyl group such as the benzoyl or pyridinoyl group or a C₁₋₁₆-alkanoyl group such as the formyl, acetyl, propionyl, butanoyl, pentanoyl or hexanoyl group, an allyloxycarbonyl group, a C₁₋₁₆-alkoxycarbonyl group such as the methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, *tert*.butoxycarbonyl, pentoxy carbonyl, hexyloxycarbonyl, octyloxycarbonyl, nonyloxycarbonyl, decyloxycarbonyl, undecyloxycarbonyl, dodecyloxycarbonyl or hexadecyloxycarbonyl group, a phenyl-C₁₋₆-alkoxycarbonyl group such as the benzyloxycarbonyl,

phenylethoxycarbonyl or phenylpropoxycarbonyl group, a C₁₋₃-alkylsulphonyl-C₂₋₄-alkoxycarbonyl, C₁₋₃-alkoxy-C₂₋₄-alkoxy-C₂₋₄-alkoxycarbonyl or R_eCO-O-(R_fCR_g)-O-CO group wherein

5 R_e denotes a C₁₋₈-alkyl, C₅₋₇-cycloalkyl, phenyl or phenyl-C₁₋₃-alkyl group,

R_f denotes a hydrogen atom, a C₁₋₃-alkyl, C₅₋₇-cycloalkyl or phenyl group and

10 R_g denotes a hydrogen atom, a C₁₋₃-alkyl or R_eCO-O-(R_fCR_g)-O group
wherein R_e to R_g are as hereinbefore defined,

while additionally the phthalimido group is a possibility for an amino group, and the above-mentioned ester groups may also be used as groups which can be converted into a carboxy group *in vivo*.

15 The residues and substituents described above may be mono- or polysubstituted by fluorine as described. Preferred fluorinated alkyl groups are fluoromethyl, difluoromethyl and trifluoromethyl. Preferred fluorinated alkoxy groups are fluoromethoxy, difluoromethoxy and trifluoromethoxy. Preferred fluorinated
20 alkylsulphanyl and alkylsulphonyl groups are trifluoromethylsulphanyl and trifluoromethylsulphonyl.

The compounds of general formula I according to the invention may have acid groups, predominantly carboxyl groups, and/or basic groups such as e.g. amino
25 functions. Compounds of general formula I may therefore be present as internal salts, as salts with pharmaceutically useable inorganic acids such as hydrochloric acid, sulphuric acid, phosphoric acid, sulphonic acid or organic acids (such as for example maleic acid, fumaric acid, citric acid, tartaric acid or acetic acid) or as salts with pharmaceutically useable bases such as alkali or alkaline earth metal
30 hydroxides or carbonates, zinc or ammonium hydroxides or organic amines such as e.g. diethylamine, triethylamine, triethanolamine *inter alia*.

The compounds according to the invention may be obtained using methods of synthesis which are known in principle. Preferably the compounds are obtained analogously to the methods of preparation described more fully hereinafter, which

5 are also a subject of this invention. Abbreviations used hereinafter are defined in the introduction to the experimental section or are familiar to those skilled in the art. The term alkyl used in reaction plans A, B and C denotes C₁₋₄-alkyl, unless otherwise stated.

10 10 If the starting materials or intermediate products listed below contain groups R¹, R², R³, X, Y, Z, A or B with amine functions, these are preferably used in protected form, for example with a Boc, Fmoc or Cbz protective group, and liberated at the end of the reactions by standard methods.

15 15 According to general reaction plan A an alkyl haloacetate (A-1), preferably optionally substituted ethyl bromoacetate, is reacted with a hydroxy compound (A-2), for example a phenol, in a molar ratio of 1:1 to 2:1 in a suitable solvent in the presence of a suitable base. Suitable bases are particularly tertiary amines such as triethylamine or Hünig base as well as alkali metal carbonates, for

20 20 example potassium carbonate. The reactions are carried out in a suitable solvent, while DMF is preferably used.

The reaction takes place in a period of from 4 to 24 hours in a temperature range from RT to 120 °C, preferably from 60 °C to 100 °C.

25 25 The alkyl aryloxy-acetates (A-3) thus obtained, after being purified, are hydrolysed to form the corresponding aryloxy-acetic acids (A-4). The reaction is preferably carried out in ethanol-water mixtures in the presence of an excess of alkali metal hydroxides, for example 2-5 equiv. sodium hydroxide. The reaction is carried out over a period of from 1 to 4 hours in a temperature range from RT to 80 °C.

30

The aryloxy-acetic acids (A-4) after purification are coupled with an aniline (A-5) to form the amide (A-6). The necessary activation of the acetic acid is preferably carried out using a mixed anhydride or using coupling reagents.

5 The mixed anhydride of the relevant aryloxy-acetic acid (A-4) is preferably prepared by reacting the acetic acid with an excess of alkyl chloroformate, preferably isopropyl chloroformate, in a molar ratio of 1:1 to 1:1.2. The bases used are preferably tertiary amines, for example N-methylmorpholine, used in equimolar amounts to the alkyl chloroformate in question.

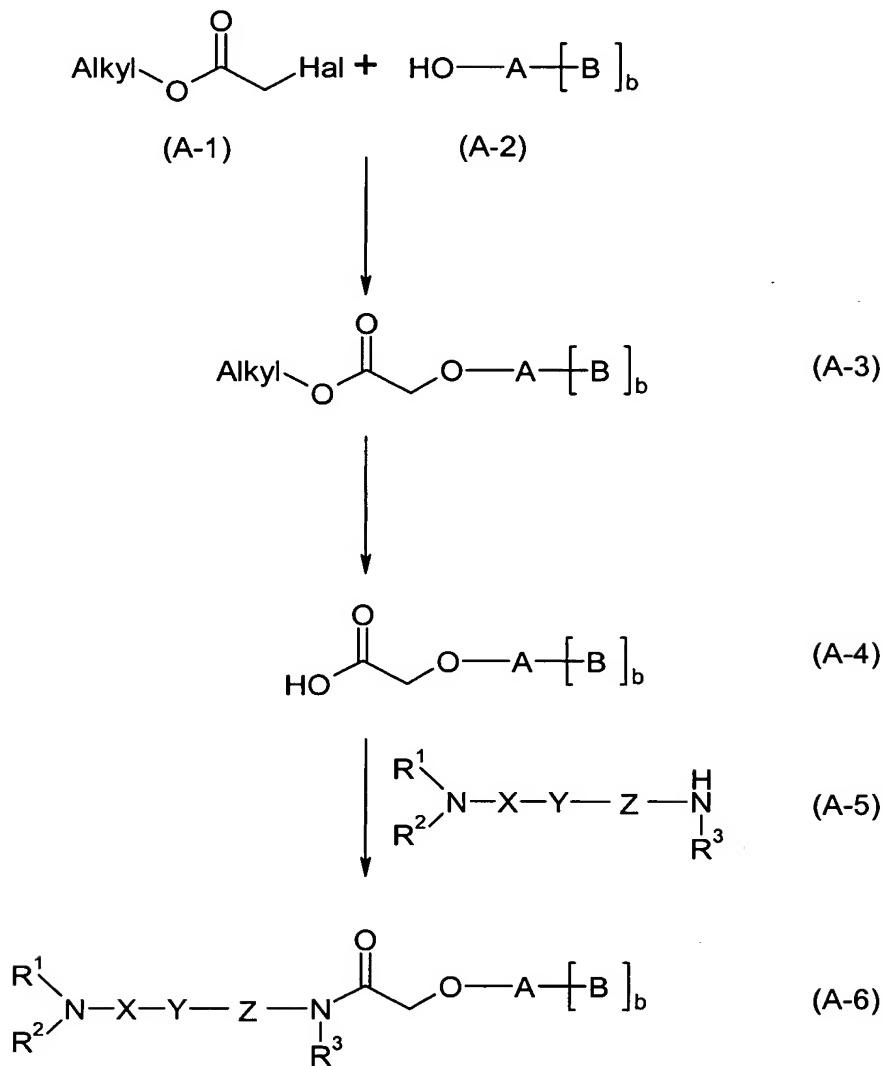
10 The reaction is carried out in a suitable solvent such as THF at temperatures between -10 °C and -5 °C and takes place over a period of 10 to 30 minutes.

The mixed anhydride thus obtained is preferably reacted with an amine compound (A-5), for example an aniline, without further purification. The aniline is used in excess relative to the particular acetic acid (A-4), preferably 5-10 mol%,.

15 The reaction is carried out for example at RT over a period of 1 to 4 hours. Another preferred reaction yields the amide (A-6) by coupling the aniline (A-5) to the corresponding aryloxy-acetic acid (A-4) with the aid of peptide coupling reagents in a suitable solvent using a suitable base. The aryloxy-acetic acid (A-4) and an aniline (A-5) are preferably used in a molar ratio of from 1.5:1 to 1:1.5. The peptide coupling reagent used is TBTU, for example, used in an equimolar amount or in excess, preferably from equimolar to a 50 mol% excess. Alternatively, the reaction may also be carried out in the presence of an amount of HOBt equimolar to the TBTU. Preferred solvents are THF and DMF in a temperature range from

20 RT to 80 °C, preferably from RT to 40 °C.

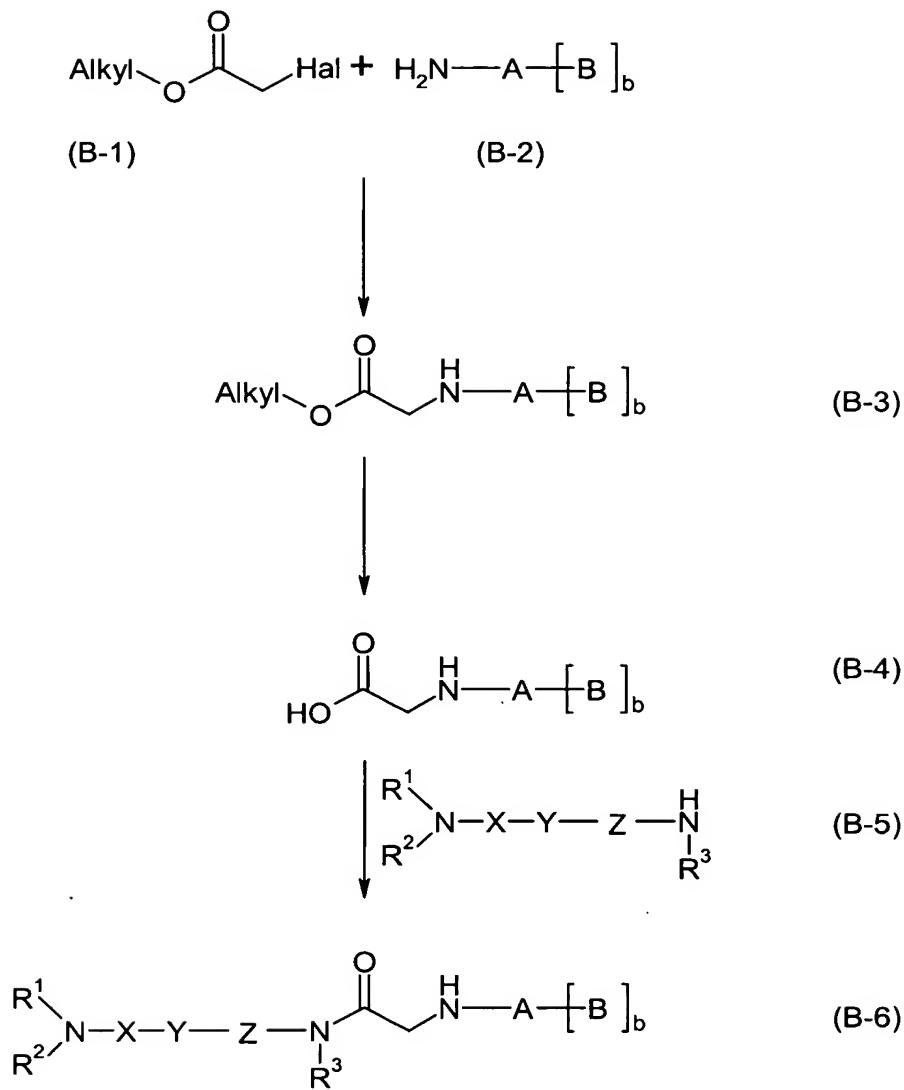
25 The bases used are preferably tertiary amines such as triethylamine or Hünig base.

Reaction plan A: (W representing -CH₂-O-)

5 According to general reaction plan B an alkyl haloacetate (B-1), preferably ethyl bromoacetate, is reacted with an amine compound (B-2), for example an aniline, in an excess, preferably in a molar ratio of 1:1 to 1.2:1, in a suitable solvent in the presence of a suitable base. Suitable bases are, in particular, tertiary amines such as Hünig base.

The solvent used is preferably Hünig base, DMF or the mixtures thereof. The reaction is carried out over a period of 4 to 48 hours in a temperature range from 90 °C to 130 °C. The further reaction of the ethyl arylamino-acetate (B-3) was carried out analogously to the general reaction plan A by hydrolysis to form the 5 arylamino-acetic acid (B-4). The amide (B-6) is preferably prepared from the acetic acid (B-4) and the aniline (B-5) using TBTU and a suitable base in a suitable solvent. The aryloxy-acetic acid (B-4) and the aniline (B-5) are preferably used in a molar ratio of 1.5:1 to 1:1.5. The peptide coupling reagent used is TBTU, for example, which is used in an equimolar amount or in excess, preferably from 10 equimolar to a 50 mol% excess. The preferred solvent is DMF in a temperature range from RT to 80 °C, preferably from RT to 40 °C. The bases used are preferably tertiary amines such as Hünig base.

Reaction plan B: (W representing -CH₂-NR⁸- with R⁸ = H in this instance)



According to reaction plan C an acrylic acid ester (C-3), e.g. an optionally substituted ethyl phenylacrylate, is prepared by palladium-catalysed reaction of an alkyl acrylate (C-1) and a (hetero)aryl halide (C-2). Preferably (hetero)arylbromide and (hetero)aryliodide (C-2) are added to the reaction in excess in relation to the acrylic acid, preferably in a molar ratio of 1:1 to 1:1.5. The solvent used may be for example acetonitrile at 80 °C. The palladium catalyst used is preferably

5

palladium(II)acetate (1 mol%) combined with tri-o-tolylphosphine (3 to 4 mol%). Suitable bases are tertiary amines such as triethylamine.

After purification, the acrylic acid ester (C-3) is hydrolysed to form the

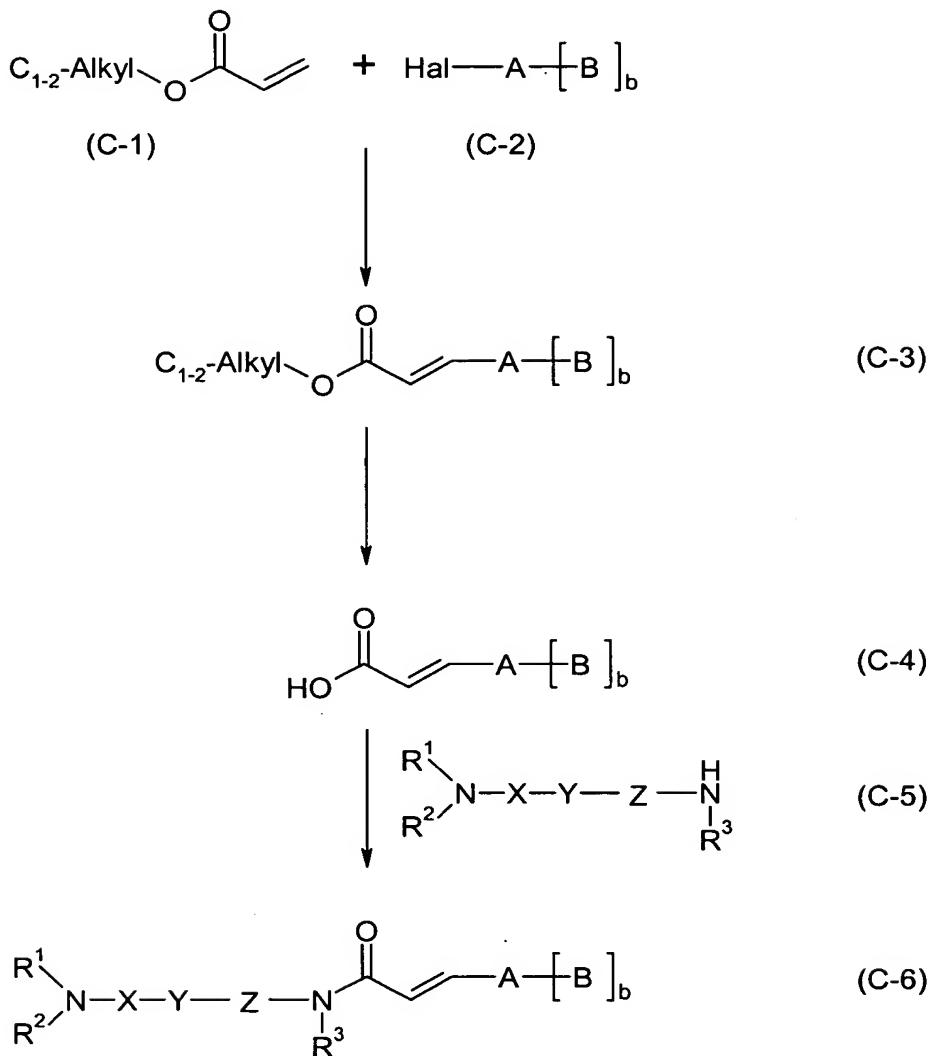
5 corresponding acrylic acid (C-4). The reaction is preferably carried out in ethanol-water mixtures in the presence of alkali metal hydroxides such as sodium hydroxide (200-300 mol%).

The reaction takes place over a period of 1 to 4 hours at ambient temperature.

10 After purification, the acrylic acid compound (C-4) is coupled to an amine compound (C-5), for example an aniline, to form the acrylamide (C-6). The necessary activation of the acrylic acid (C-4) takes place analogously to general reaction plan A, preferably via a mixed anhydride or using coupling reagents such as TBTU or TBTU in combination with HOBr.

15

Reaction plan C: (W representing -CH=CH-)



The compounds according to the invention may advantageously also be obtained
5 using methods described in the following Examples, which may also be combined
with methods known to the skilled man from the literature, for example.

Stereoisomeric compounds of formula (I) may be separated in principle by
conventional methods. The diastereomers may be separated on the basis of their
10 different physico-chemical properties, e.g. by fractional crystallisation from suitable

solvents, by high pressure liquid or column chromatography, using chiral or preferably non-chiral stationary phases.

Racemates covered by general formula (I) may be separated for example by
5 HPLC on suitable chiral stationary phases (e.g. Chiral AGP, Chiraldpak AD). Racemates which contain a basic or acidic function can also be separated via the diastereomeric, optically active salts which are produced on reacting with an optically active acid, for example (+) or (-)-tartaric acid, (+) or (-)-diacetyl tartaric acid, (+) or (-)-monomethyl tartrate or (+)-camphorsulphonic acid, or an optically
10 active base, for example with (R)-(+)-1-phenylethylamine, (S)-(-)-1-phenylethylamine or (S)-brucine.

According to a conventional method of separating isomers, the racemate of a compound of general formula (I) is reacted with one of the above-mentioned
15 optically active acids or bases in equimolar amounts in a solvent and the resulting crystalline, diastereomeric, optically active salts thereof are separated using their different solubilities. This reaction may be carried out in any type of solvents provided that they show sufficient differences in terms of the solubility of the salts. Preferably, methanol, ethanol or mixtures thereof, for example in a ratio by volume
20 of 50:50, are used. Then each of the optically active salts is dissolved in water, carefully neutralised with a base such as sodium carbonate or potassium carbonate, or with a suitable acid, e.g. with dilute hydrochloric acid or aqueous methanesulphonic acid, and in this way the corresponding free compound is obtained in the (+) or (-) form.

25 The (R) or (S) enantiomer alone or a mixture of two optically active diastereomeric compounds covered by general formula I may also be obtained by performing the syntheses described above with a suitable reaction component in the (R) or (S) configuration.

30

As already mentioned, the compounds of formula (I) may be converted into the salts thereof, particularly for pharmaceutical use into the physiologically and pharmacologically acceptable salts thereof. These salts may be present on the one hand as physiologically and pharmacologically acceptable acid addition salts

5 of the compounds of formula (I) with inorganic or organic acids. On the other hand, in the case of acidically bound hydrogen, the compound of formula (I) may also be converted by reaction with inorganic bases into physiologically and pharmacologically acceptable salts with alkali or alkaline earth metal cations as counter-ion. The acid addition salts may be prepared, for example, using

10 hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, ethanesulphonic acid, toluenesulphonic acid, benzenesulphonic acid, acetic acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid or maleic acid. Moreover, mixtures of the above mentioned acids may be used. To prepare the alkali and alkaline earth metal salts of the compound

15 of formula (I) with acidically bound hydrogen the alkali and alkaline earth metal hydroxides and hydrides are preferably used, while the hydroxides and hydrides of the alkali metals, particularly sodium and potassium are preferred and sodium and potassium hydroxide are most preferred.

20 The compounds according to the present invention, including the physiologically acceptable salts, are effective as antagonists of the MCH receptor, particularly the MCH-1 receptor, and exhibit good affinity in MCH receptor binding studies. Pharmacological test systems for MCH-antagonistic properties are described in the following experimental section.

25 As antagonists of the MCH receptor the compounds according to the invention are advantageously suitable as pharmaceutical active substances for the prevention and/or treatment of symptoms and/or diseases caused by MCH or causally connected with MCH in some other way. Generally the compounds

30 according to the invention have low toxicity, they are well absorbed by oral route and have an intracerebral transitivity, particularly brain accessibility.

Therefore, MCH antagonists which contain at least one compound according to the invention, are particularly suitable in mammals, such as for example rats, mice, guinea pigs, hares, dogs, cats, sheep, horses, pigs, cattle, monkeys and also 5 humans, for the treatment and/or prevention of symptoms and/or diseases which are caused by MCH or are otherwise causally connected with MCH.

Diseases caused by MCH or otherwise causally connected with MCH are particularly metabolic disorders, such as for example obesity, and eating 10 disorders, such as for example bulimia, including bulimia nervosa. The indication obesity includes in particular exogenic obesity, hyperinsulinaemic obesity, hyperplasmic obesity, hyperphyseal adiposity, hypoplasmic obesity, hypothyroid obesity, hypothalamic obesity, symptomatic obesity, infantile obesity, upper body obesity, alimentary obesity, hypogonadal obesity and central obesity. This range 15 of indications also includes cachexia, anorexia and hyperphagia.

Compounds according to the invention may, in particular, be suitable for reducing hunger, curbing appetite, controlling eating behaviour and/or promoting a feeling of satiety.

20 In addition, the diseases caused by MCH or otherwise causally connected with MCH also include hyperlipidaemia, cellulitis, fat accumulation, malignant mastocytosis, systemic mastocytosis, emotional disorders, affectivity disorders, depression, anxiety states, sleep disoreders, reproductive disorders, sexual 25 disorders, memory disorders, epilepsy, forms of dementia and hormonal disorders.

Compounds according to the invention are also suitable as active substances for the prevention and/or treatment of other illnesses and/or disorders, particularly those which accompany obesity, such as, for example, diabetes, diabetes mellitus, 30 especially type II diabetes, hyperglycaemia, particularly chronic hyperglycaemia, complications of diabetes including diabetic retinopathy, diabetic neuropathy,

diabetic nephropathy, etc., insulin resistance, pathological glucose tolerance, encephalorrhagia, cardiac insufficiency, cardiovascular diseases, particularly arteriosclerosis and high blood pressure, arthritis and gonitis.

5 MCH antagonists and formulations according to the invention may advantageously be used in combination with a dietary therapy, such as for example a dietary diabetes treatment, and exercise.

Another range of indications for which the compounds according to the invention
10 are advantageously suitable is the prevention and/or treatment of urinary disorders, such as for example urinary incontinence, overactive bladder, urgency, nycturia and enuresis, while the Harninkontinenz, überaktiver Harnblase, Harndrang, Nykturie, Enuresis, while the overactive bladder and urgency may or may not be connected with benign prostatic hyperplasia.

15 The dosage required to achieve such an effect is conveniently, by intravenous or subcutaneous route, 0.001 to 30 mg/kg of body weight, preferably 0.01 to 5 mg/kg of body weight, and by oral or nasal route or by inhalation, 0.01 to 50 mg/kg of body weight, preferably 0.1 to 30 mg/kg of body weight, in each case once to three
20 times a day.

For this purpose, the compounds of formula I prepared according to the invention
25 may be formulated, optionally together with other active substances as described hereinafter, together with one or more inert conventional carriers and/or diluents, e.g. with corn starch, lactose, glucose, microcrystalline cellulose, magnesium stearate, polyvinylpyrrolidone, citric acid, tartaric acid, water, water/ethanol, water/glycerol, water/sorbitol, water/polyethylene glycol, propylene glycol, cetylstearyl alcohol, carboxymethylcellulose or fatty substances such as hard fat or suitable mixtures thereof, to produce conventional galenic preparations such as
30 plain or coated tablets, capsules, powders, granules, solutions, emulsions, syrups, aerosols for inhalation, ointments or suppositories.

In addition to pharmaceutical compositions the invention also covers compositions containing at least one amide compound according to the invention and/ or a salt according to the invention optionally together with one or more physiologically acceptable excipients. Such compositions may also be foods, for example, which may be solid or liquid, in which the compound according to the invention is incorporated.

For the above mentioned combinations it is possible to use as additional active substances particularly those which for example potentiate the therapeutic effect of an MCH antagonist according to the invention in terms of one of the indications mentioned above and/or which make it possible to reduce the dosage of an MCH antagonist according to the invention. Preferably one or more additional active substances are selected from among

- 15 - active substances for the treatment of diabetes,
- active substances for the treatment of diabetic complications,
- active substances for the treatment of obesity, preferably other than MCH antagonists,
- active substances for the treatment of high blood pressure,
- 20 - active substances for the treatment of hyperlipidaemia, including arteriosclerosis,
- active substances for the treatment of arthritis,
- active substances for the treatment of anxiety states,
- active substances for the treatment of depression.

25

The above mentioned categories of active substances will now be explained in more detail by means of examples.

Examples of active substances for the treatment of diabetes are insulin sensitisers, insulin secretion accelerators, biguanides, insulins, α -glucosidase inhibitors, β 3 adreno-receptor agonists.

5 Insulin sensitisers include pioglitazone and its salts (preferably hydrochloride), troglitazone, rosiglitazone and its salts (preferably maleate), JTT-501, GI-262570, MCC-555, YM-440, DRF-2593, BM-13-1258, KRP-297, R-119702, GW-1929.

10 Insulin secretion accelerators include sulphonylureas, such as for example tolbutamide, chloropropamide, tolzamide, acetohexamide, gliclazide, glycopyramide and its ammonium salts, glibenclamide, gliclazide, glimepiride. Further examples of insulin secretion accelerators are repaglinide, nateglinide, mitiglinide (KAD-1229) and JTT-608.

Biguanides include metformin, buformin and phenformin.

15 Insulins include those obtained from animals, particularly cattle or pigs, semisynthetic human insulins which are synthesised enzymatically from insulin obtained from animals, human insulin obtained by genetic engineering, e.g. from Escherichia coli or yeasts. Moreover, the term insulin also includes insulin-zinc (containing 0.45 to 0.9 percent by weight of zinc) and protamine-insulin-zinc obtainable from zinc chloride, protamine sulphate and insulin. Insulation may also be obtained from insulin fragments or derivatives (for example INS-1, etc.).

20 Insulin may also include different kinds, e.g. with regard to the onset time and duration of effect ("ultra immediate action type", "immediate action type", "two phase type", "intermediate type", "prolonged action type", etc.), which are selected depending on the pathological condition of the patient.

25 α -Glucosidase inhibitors include acarbose, voglibose, miglitol, emiglitatide.

30

β_3 Adreno receptor agonists include AJ-9677, BMS-196085, SB-226552, AZ40140.

5 Active substances for the treatment of diabetes other than those mentioned above include ergoset, pramlintide, leptin, BAY-27-9955 as well as glycogen phosphorylase inhibitors, sorbitol dehydrogenase inhibitors, protein tyrosine phosphatase 1B inhibitors, dipeptidyl protease inhibitors, glipizid, glyburide.

10 Active substances for the treatment of diabetic complications include for example aldose reductase inhibitors, glycation inhibitors and protein kinase C inhibitors.

Aldose reductase inhibitors are for example tolrestat, epalrestat, imirestat, zenarestat, SNK-860, zopolrestat, ARI-50i, AS-3201.

15 An example of a glycation inhibitor is pimagedine.

Protein Kinase C inhibitors are for example NGF, LY-333531.

20 Active substances other than those mentioned above for the treatment of diabetic complications include alprostadil, thiapride hydrochloride, cilostazol, mexiletine hydrochloride, ethyl eicosapentate, memantine, pimagedine (ALT-711).

25 Active substances for the treatment of obesity, preferably other than MCH antagonists, include lipase inhibitors and anorectics.

A preferred example of a lipase inhibitor is orlistat.

30 Examples of preferred anorectics are phentermine, mazindol, dextroamphetamine, fluoxetine, sibutramine, bupropion, (S)-sibutramine, SR-141716, NGD-95-1.

Active substances other than those mentioned above for the treatment of obesity include lipstatin.

5 Moreover for the purposes of this application the active substance group of anti-obesity active substances also includes the anorectics, of which the β_3 agonists, thyromimetic active substances and NPY antagonists should be emphasised. The scope of the anti-obesity or anorectic active substances which are preferred here is indicated by the following additional list, by way of example: phenylpropanolamine, ephedrine, pseudoephedrine, phentermine, a cholecystokinin-A (hereinafter referred to as CCK-A) agonist, a monoamine reuptake inhibitor (such as for example sibutramine), a sympathomimetic active substance, a serotonergic active substance (such as for example dextfenfluramine or fenfluramine), a dopamine antagonist (such as for example bromocriptine), a melanocyte-stimulating hormone receptor agonist or mimetic, an analogue of melanocyte-stimulating hormone, a cannabinoid receptor antagonist, an MCH antagonist, the OB protein (hereinafter referred to as leptin), a leptin analogue, a leptin receptor agonist, a galanine antagonist, a GI lipase inhibitor or reducer (such as for example orlistat).

10 Other anorectics include bombesin agonists, dehydroepiandrosterone or its analogues, glucocorticoid receptor agonists and antagonists, orexin receptor antagonists, urocortin binding protein antagonists, agonists of the Glucagon-like Peptide-1 receptor, such as for example exendin and ciliary neurotrophic factors, such as for example axokine.

15

20

25 Active substances for the treatment of high blood pressure include inhibitors of angiotensin converting enzyme, calcium antagonists, potassium channel openers and angiotensin II antagonists.

Inhibitors of angiotensin converting enzyme include captopril, enalapril, alacepril, delapril (hydrochloride), lisinopril, imidapril, benazepril, cilazapril, temocapril, trandolapril, manidipine (hydrochloride).

5 Examples of calcium antagonists are nifedipine, amlodipine, efonidipine, nicardipine.

Potassium channel openers include levcromakalim, L-27152, AL0671, NIP-121.

10 Angiotensin II antagonists include telmisartan, losartan, candesartan cilexetil, valsartan, irbesartan, CS-866, E4177.

15 Active substances for the treatment of hyperlipidaemia, including arteriosclerosis, include HMG-CoA reductase inhibitors, fibrate compounds.

HMG-CoA reductase inhibitors include pravastatin, simvastatin, lovastatin, atorvastatin, fluvastatin, lipantil, cerivastatin, itavastatin, ZD-4522 and the salts thereof.

20 Fibrate compounds include bezafibrate, clinofibrate, clofibrate and simfibrate.

Active substances for the treatment of arthritis include ibuprofen.

25 Active substances for the treatment of anxiety states include chlordiazepoxide, diazepam, oxazepam, medazepam, cloxazolam, bromazepam, lorazepam, alprazolam, fludiazepam.

30 Active substances for the treatment of depression include fluoxetine, fluvoxamine, imipramine, paroxetine, sertraline.

The dosage for these active substances is conveniently 1/5 of the lowest normal recommended dose up to 1/1 of the normal recommended dose.

In another embodiment the invention also relates to the use of at least one amide compound according to the invention and/or a salt according to the invention for influencing the eating behaviour of a mammal. This use is based particularly on the fact that compounds according to the invention may be suitable for reducing hunger, curbing appetite, controlling eating behaviour and/or promoting a feeling of satiety. The eating behaviour is advantageously influenced in such a way as to reduce food intake. Therefore, the compounds according to the invention are advantageously used for reducing body weight. A further use according to the invention is the prevention of increases in body weight, for example in people who have previously taken steps to reduce their weight and are then interested in maintaining their reduced body weight. According to this embodiment it is preferably a non-therapeutic use. Such a non-therapeutic use may be a cosmetic use, for example for altering the outer appearance, or an application for improving the general feeling of wellbeing. The compounds according to the invention are preferably used in a non-therapeutic capacity for mammals, particularly humans, who have no diagnosed disorders of eating behaviour, no diagnosed obesity, bulimia, diabetes and/ or no diagnosed urinary problems, particularly urinary incontinence. Preferably the compounds according to the invention are suitable for non-therapeutic use in humans whose body mass index (BMI = body mass index), which is defined as the body weight measured in kilograms divided by the height (in metres) squared, is less than 30, particularly less than 25.

25

The Examples that follow are intended to illustrate the invention:

Preliminary remarks:

As a rule, IR, $^1\text{H-NMR}$ and/or mass spectra have been obtained for the compounds prepared. Unless otherwise stated the R_f values are determined using ready-made silica gel 60 TLC plates F₂₅₄ (E. Merck, Darmstadt, Item no.

5 1.05714) without chamber saturation. The R_f values obtained under the name Alox are determined using ready-made aluminium oxide 60 F₂₅₄ TLC plates (E. Merck, Darmstadt, Item no. 1.05713) without chamber saturation. The ratios given for the eluants relate to units by volume of the solvent in question. The units by volume for NH₃ relate to a concentrated solution of NH₃ in water. Silica gel made by
10 Millipore (MATREXTM, 35-70 my) is used for chromatographic purification. Alox (E. Merck, Darmstadt, aluminium oxide 90 standardised, 63-200 μm , Item no. 1.01097.9050) is used for chromatographic purification. The HPLC data given are measured under the following parameters:
Analytical columns: Zorbax column (Agilent Technologies), SB (Stable Bond) -
15 C18; 3.5 μm ; 4.6 x 75 mm; column temperature: 30°C; flow: 0.8 mL / min; injection volume: 5 μL ; detection at 254 nm (methods A and B)
Symmetry 300 (Waters), 3.5 μm ; 4.6 x 75 mm; column temperature: 30°C; flow:
0.8 mL / min; injection volume: 5 μL ; detection at 254 nm (method C)
method A: water:acetonitrile:formic acid 9:1:0.01 to 1:9:0.01 over 9 min
20 method B: water:acetonitrile:formic acid 9:1:0.01 to 1:9:0.01 over 4 min, then 6 min 1:9:0.01
method C: water:acetonitrile:formic acid 9:1:0.01 to 1:9:0.01 over 4 min, then 6 min 1:9:0.01
Preparative column: Zorbax column (Agilent Technologies), SB (Stable Bond) -
25 C18; 3.5 μm ; 30 x 100 mm; column temperature: ambient temperature; flow: 30 mL / min; detection at 254 nm.
In preparative HPLC purifications, as a rule, the same gradients are used as were used to raise the analytical HPLC data.
The products are collected under mass control, the fractions containing product
30 are combined and freeze-dried.

If there is no specific information as to the configuration, it is not clear whether there are pure enantiomers or whether partial or even total racemisation has taken place.

5

The following abbreviations are used above and hereinafter:

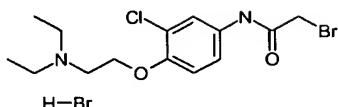
	abs.	absolute
	Boc	<i>tert</i> -butoxycarbonyl
	Cbz	benzyloxycarbonyl
10	CDI	N,N'-carbonyldiimidazole
	CDT	1,1'-carbonyldi(1,2,4-triazole)
	DMF	N,N-dimethylformamide
	ether	diethyl ether
	EtOAc	ethyl acetate
15	EtOH	ethanol
	Fmoc	9-fluorenylmethoxycarbonyl
	sat.	saturated
	semiconc.	semiconcentrated
	HCl	hydrochloric acid
20	HOAc	acetic acid
	HOBr	1-hydroxybenzotriazole-hydrate
	Hünig base	N-ethyldiisopropylamine
	HV	high vacuum
	i. vac.	in vacuo (in vacuo)
25	KOH	potassium hydroxide
	conc.	concentrated
	MeOH	methanol
	MTBE	methyl- <i>tert</i> -butylether
	NaCl	sodium chloride
30	NaOH	sodium hydroxide
	org.	organic

Ph	phenyl
RT	ambient temperature (ca. 20°C)
TBTU	2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium-tetrafluoroborate
5 TEBAC	triethylbenzylammonium chloride
TFA	trifluoroacetic acid
THF	tetrahydrofuran
→*	denotes the binding site of a group

10

Synthesis of intermediate products

5 Intermediate product 1:



Z1a) [2-(2-chloro-4-nitro-phenoxy)-ethyl]-diethyl-amine-hydrobromide

40.00 g (1.00 mol) of potassium carbonate was added to a solution of 50.00 g

(0.288 mol) of 2-chloro-4-nitro-phenol and 60.23 g (0.350 mol) of (2-chloro-ethyl)-

10 diethyl-amine in 700 mL DMF and the mixture was stirred for 16 hours at 80°C. The reaction mixture was evaporated down i. vac., the residue was combined with water and the aqueous phase was exhaustively extracted with EtOAc. The combined org. extracts were washed with water, dried over magnesium sulphate and evaporated down i. vac. The crude product was recrystallised from EtOAc
15 and the mother liquor evaporated down i. vac. Purification of the residue by column chromatography (silica gel, gradient dichloromethane / MeOH 10:0 → 9:1) yielded the desired product.

Yield: 29.00 g (37 % of theory)

$C_{12}H_{17}ClN_2O_3$ ($M = 272.734$)

20 Calc.: molpeak ($M+H$)⁺: 273/275

Found: molpeak ($M+H$)⁺: 273/275 (Cl)

Z1b) 3-chloro-4-(2-diethylamino-ethoxy)-phenylamine

A solution of 100 mL of conc. aqueous HCl in 100 mL EtOH was added dropwise

25 to a suspension of 20.00 g (358 mmol) of iron powder and 20 g (73.33 mmol) of [2-(2-chloro-4-nitro-phenoxy)-ethyl]-diethyl-amine in 200 mL EtOH, while the temperature was kept below 20 °C by cooling with ice. The reaction mixture was stirred for 30 minutes, neutralised with 10% aqueous sodium bicarbonate solution

and was exhaustively extracted with EtOAc. The combined org. extracts were dried over magnesium sulphate and evaporated down i. vac. The product was stored under a nitrogen atmosphere.

Yield: 17.40 g (98 % of theory)

5 C₁₂H₁₉CIN₂O (M= 242.751)

Calc.: molpeak(M+H)⁺: 243/245

Found: molpeak (M+H)⁺: 243/245 (Cl)

R_f value: 0.6 (silica gel, dichloromethane / MeOH / conc. aqueous ammonia 90:10:1)

10

Z1c) 2-bromo-N-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-acetamide-hydrobromide

A solution of 1.86 mL (21.00 mmol) of bromoacetyl bromide in 10 mL of dichloromethane was added dropwise to a solution of 5.00 g (21.00 mmol) of 3-chloro-4-(2-diethylamino-ethoxy)-phenylamine in 100 mL of dichloromethane at 0 °C and the mixture was stirred for 20 minutes at 0 °C. The precipitate formed was filtered off, washed with dichloromethane and MTBE and dried i. vac. at 40 °C.

Yield: 8.20 g (89 % of theory)

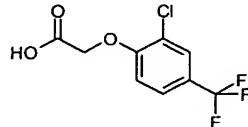
C₁₄H₂₁BrCIN₂O₂ * Br (M= 444.597)

20 Calc.: molpeak(M+H)⁺: 363/365/367

Found: molpeak (M+H)⁺: 363/365/367 (BrCl)

HPLC-MS: 4.2 for 5 min. (Stable Bond C18; 3.5 µm; water:acetonitrile:formic acid 9:1:0.01 → 1:9:0.01 over 9 min)

25 Intermediate product 2:



Z2a) ethyl (2-chloro-4-trifluoromethyl-phenoxy)-acetate

28.19 g (0.204 mol) of potassium carbonate was added to a solution of 20.00 g (0.102 mol) of 2-chloro-4-trifluoromethyl-phenol and 11.36 mL (0.102 mol) of ethyl bromo-acetate in 300 mL of DMF and the mixture was stirred for 7 hours at 60 °C and for 16 hours at RT. The reaction mixture was evaporated down i. vac. and the residue combined with EtOAc. The org. phase was washed with water, dried over magnesium sulphate and evaporated down i. vac.

5 Yield: 23.79 g (83% of theory)

$C_{11}H_{10}ClF_3O_3$ ($M= 282.649$)

Calc.: molpeak($M+Na^+$): 305/307

10 Found: molpeak ($M+Na^+$): 305/307 (Cl)

R_f value: 0.58 (silica gel, petroleum ether / EtOAc 4:1)

Z2b) (2-chloro-4-trifluoromethyl-phenoxy)-acetic acid

84 mL of 2 M aqueous NaOH was added to a solution of 23.97 g (0.084 mol) of 15 ethyl (2-chloro-4-trifluoromethyl-phenoxy)-acetate in 200 mL EtOH and the mixture was refluxed for 1 hour. EtOH was concentrated by evaporation i. vac., the residue was diluted with ice water and acidified with 2 M aqueous HCl. The precipitate formed was filtered off, washed with water and dried at 70 °C i. vac.

Yield: 12.33 g (58 % of theory)

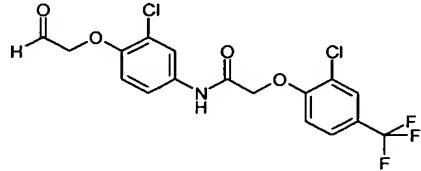
20 $C_9H_6ClF_3O_3$ ($M= 254.595$)

Calc.: molpeak($M-H^-$): 253/255

Found: molpeak ($M-H^-$): 253/255 (Cl)

R_f value: 0.04 (silica gel, petroleum ether /EtOAc 3:2)

25 Intermediate product 3:



Z3a) 2-chloro-1-(2,2-diethoxyethoxy)-4-nitrobenzene

26.56 g (0.150 mol) of 2-chloro-4-nitrophenol and 24.25 mL (0.150 mol) of 2-bromo-1,1-diethoxy-ethane was added to a suspension of 22.80 g (0.165 mol) of potassium carbonate in 250 mL DMF and the mixture was heated to 140 °C for 24 hours. The reaction mixture was diluted with 1 L water and exhaustively extracted
 5 with MTBE. The combined org. extracts were washed with water, dried over magnesium sulphate and evaporated down i. vac. Yield: 32.10 g (74 % of theory)
 $C_{12}H_{16}ClNO_5$ (M= 289.718)

R_f value: 0.7 (silica gel, dichloromethane / cyclohexane / EtOAc 1:4:1)

10 Z3b) 3-chloro-4-(2,2-diethoxy-ethoxy)-phenylamine

30 g (0.104 mol) of 2-chloro-1-(2,2-diethoxy-ethoxy)-4-nitrobenzene was added to a suspension of 1.50 g Pd/C (10 %) in 500 mL EtOAc and the mixture was hydrogenated for 2 hours at 20 psi. The catalyst was filtered off and the filtrate evaporated down i. vac.

15 Yield: 27.00 g (quantitative yield)

$C_{12}H_{18}ClNO_3$ (M= 259.735)

Calc.: molpeak(M+H)⁺: 260/262

Found: molpeak (M+H)⁺: 260/262 (Cl)

R_f value: 0.75 (silica gel, dichloromethane / MeOH 9:1)

20

Z3c) N-[3-chloro-4-(2,2-diethoxy-ethoxy)-phenyl]-2-(2-chloro-4-trifluoromethyl-phenoxy)-acetamide

4.495 g (0.028 mol) of CDI was added to a solution of 6.365 g (0.025 mol) of (2-chloro-4-trifluoromethyl-phenoxy)-acetic acid (intermediate product 2b) in 100 mL

25 abs. THF and the mixture was stirred for 30 minutes at 50 °C. 6.494 g (0.025 mol) of 3-chloro-4-(2,2-diethoxy-ethoxy)-phenylamine was added and the mixture was stirred for 16 hours at RT. The reaction mixture was poured into ice water and stirred for 1 hour. The precipitate formed was filtered off, washed with water and dried at 50 °C.

30 Yield: 11.40 g (92 % of theory)

$C_{21}H_{22}Cl_2F_3NO_5$ (M= 496.314)

Calc.: molpeak(M-H)⁻: 494/496/498

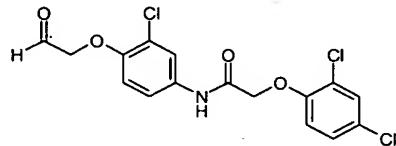
Found: molpeak (M-H)⁻: 494/496/498 (Cl₂)

R_f value: 0.73 (silica gel, petroleum ether /EtOAc 3:2)

5 Z3d) N-[3-chloro-4-(2-oxo-ethoxy)-phenyl]-2-(2-chloro-4-trifluoromethyl-phenoxy)-acetamide
 40 mL water and 130 mL TFA was added to a solution of 11.40 g (0.023 mol) of N-[3-chloro-4-(2,2-diethoxy-ethoxy)-phenyl]-2-(2-chloro-4-trifluoromethyl-phenoxy)-acetamide in 130 mL chloroform at 0 °C and the mixture was stirred for 3.5 hours
 10 at 0 °C and for 48 hours at RT. The reaction mixture was neutralised with sat. aqueous sodium carbonate solution and exhaustively extracted with dichloromethane. The combined org. extracts were washed with water, dried over magnesium sulphate and evaporated down i. vac.
 Yield: 8.40g (86 % of theory)

15 C₁₇H₁₂Cl₂F₃NO₄(M= 422.191)
 Calc.: molpeak(M-H)⁻: 421/423/425
 Found: molpeak (M-H)⁻: 421/423/425 (Cl₂)
 R_f value: 0.14 (silica gel, petroleum ether /EtOAc 3:2)

20 Intermediate product 4:



Z4a) N-[3-chloro-4-(2,2-diethoxy-ethoxy)-phenyl]-2-(2,4-dichloro-phenoxy)-acetamide

At 0 °C a solution of 0.57 g (2.38 mmol) of (2,4-dichloro-phenoxy)-acetylchloride in
 25 4 mL dichloromethane was added dropwise to a solution of 0.50 g (2.16 mmol) of 3-chloro-4-(2,2-diethoxy-ethoxy)-phenylamine (intermediate product Z3b) and 0.74 mL (4.32 mmol) of ethyl-diisopropylamine in 10 mL dichloromethane and the

mixture was stirred for 1 hour at 0 °C. MeOH was added and the precipitated product was filtered off. The product was washed with MeOH and dried i. vac.

Yield: 0.74 g (79% of theory)

C₁₈H₁₈Cl₃NO₅ (M= 434.70)

5 Calc.: molpeak(M-H)⁻: 432/434/436

Found: molpeak (M-H)⁻: 432/434/436 (Cl₃)

HPLC-MS: 5.00 Min. (Devosil RP Aqueous; 30-100% water / acetonitrile 70:30 → 0:100 in for 5 min.)

10 Z4b) N-[3-chloro-4-(2-oxo-ethoxy)-phenyl]-2-(2,4-dichloro-phenoxy)-acetamide

At 0 °C 2 mL TFA and 0.15 mL water was added to a solution of 50 mg (0.011 mmol) of N-[3-chloro-4-(2,2-diethoxy-ethoxy)-phenyl]-2-(2,4-dichloro-phenoxy)-acetamide in 2 mL dichloromethane and the mixture was stirred for 3.5 hours. 200 ml of 2 M aqueous sodium carbonate solution was added and exhaustively

15 extracted with dichloromethane. The combined org. extracts were dried over magnesium sulphate, evaporated down i. vac. and the residue was purified by column chromatography (silica gel, EtOAc / hexane 1:1).

Yield: 40 mg (89 % of theory)

C₁₆H₁₂Cl₃NO₄ (M= 388.63)

20 Calc.: molpeak(M-H)⁻: 386/388/390

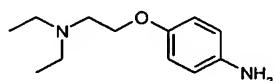
Found: molpeak (M-H)⁻: 386/388/390 (Cl₃)

R_f value: 0.25 (silica gel, hexane / EtOAc 3:2)

HPLC-MS: 4.56 Min. (Devosil RP Aqueous; 5-100% water / acetonitrile 70:30 → 0:100 in for 5 min.)

25

Intermediate product 5:



Z5a) Diethyl-[2-(4-nitro-phenoxy)-ethyl]-amine

2.07 g (15.0 mmol) of potassium carbonate was added to a solution of 1.04 g (7.5 mmol) of 4-nitrophenol in 20 mL DMF under an argon atmosphere and the mixture was stirred for 20 minutes at 80 °C. 1.72 g (10.0 mmol) of (2-chloro-ethyl)-diethyl-amine-hydrochloride was added and the mixture was stirred for 8 hours at 90 °C.

5 100 ml of 2 M aqueous sodium carbonate solution was added and exhaustively extracted with ether. The combined org. extracts were dried over magnesium sulphate and evaporated down i. vac. The crude product was used in the next reaction step without further purification.

Yield: 1.59 g (89% of theory)

10 $C_{12}H_{18}N_2O_3$ ($M= 238.28$)

Calc.: molpeak($M+H$)⁺: 239

Found: molpeak ($M+H$)⁺: 239

R_f value: 0.2 (silica gel, EtOAc)

15 Z5b) 4-(2-Diethylamino-ethoxy)-phenylamine

2.6 g (10.9 mmol) of diethyl-[2-(4-nitro-phenoxy)-ethyl]-amine was added to a suspension of 130 mg Pd/C (10 %) in 20 mL MeOH and the mixture was hydrogenated for 4 hours. The catalyst was filtered off and the filtrate evaporated down i. vac.

20 Yield: 2.19 g (96% of theory)

$C_{12}H_{20}N_2O$ ($M= 208.30$)

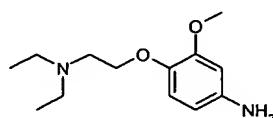
Calc.: molpeak($M+H$)⁺: 209

Found: molpeak ($M+H$)⁺: 209

R_f value: 0.2 (silica gel, dichloromethane / MeOH 9:1)

25

Intermediate product 6:



Z6a) Diethyl-[2-(2-methoxy-4-nitro-phenoxy)-ethyl]-amine

The product was obtained analogously to intermediate product Z5a starting from 1.27 g (7.5 mmol) of 2-methoxy-4-nitro-phenol and 1.72 g (10.0 mmol) of (2-chloro-ethyl)-diethyl-amine-hydrochloride.

Yield: 1.01 g (50 % of theory)

5 C₁₃H₂₀N₂O₄ (M= 268.31)

Calc.: molpeak(M+H)⁺: 269

Found: molpeak (M+H)⁺: 269

R_f value: 0.2 (silica gel, EtOAc)

10 Z6b) 4-(2-Diethylamino-ethoxy)-3-methoxy-phenylamine

0.77 g (2.87 mmol) of diethyl-[2-(2-methoxy-4-nitro-phenoxy)-ethyl]-amine was added to a suspension of 1.00 g (17.9 mmol) of iron powder in 7 mL EtOH and the mixture was stirred for 10 minutes at RT. 6.6 mL of conc. aqueous HCl was added dropwise within 15 minutes and the mixture was stirred for 1 hour. 100 ml of 2 M sodium carbonate solution was added and the mixture was exhaustively extracted with EtOAc. The combined org. extracts were dried over magnesium sulphate and evaporated down i. vac.

Yield: 0.62 g (92 % of theory)

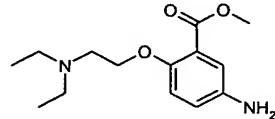
C₁₃H₂₂N₂O₂ (M= 238.33)

20 Calc.: molpeak(M+H)⁺: 269

Found: molpeak (M+H)⁺: 269

R_f value: 0.05 (silica gel, dichloromethane / MeOH 9:1)

Intermediate product 7:



25

Z7a) methyl 2-(2-diethylamino-ethoxy)-5-nitro-benzoate

The product was obtained analogously to intermediate product Z5a starting from 1.48 g (7.5 mmol) of methyl 2-hydroxy-5-nitro-benzoate and 1.72 g (10.0 mmol) of (2-chloro-ethyl)-diethyl-amine-hydrochloride.

Yield: 0.81 g (40 % of theory)

5 $C_{14}H_{20}N_2O_5$ ($M= 296.32$)

Calc.: molpeak($M+H$)⁺: 297

Found: molpeak ($M+H$)⁺: 297

R_f value: 0.1 (silica gel, EtOAc / MeOH 9:1)

10 Z7b) methyl 5-amino-2-(2-diethylamino-ethoxy)-benzoate

The product was obtained analogously to intermediate product Z5b starting from 400 mg (1.35 mmol) of methyl 2-(2-diethylamino-ethoxy)-5-nitro-benzoate.

Yield: 0.35 g (97 % of theory)

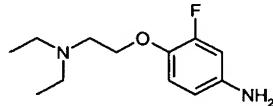
$C_{14}H_{22}N_2O_3$ ($M= 266.34$)

15 Calc.: molpeak($M+H$)⁺: 267

Found: molpeak ($M+H$)⁺: 267

R_f value: 0.2 (silica gel, EtOAc / MeOH 9:1)

Intermediate product 8:



20

Z8a) diethyl-[2-(2-fluoro-4-nitro-phenoxy)-ethyl]-amine

The product was obtained analogously to intermediate product Z5a starting from 1.18 g (7.5 mmol) of 2-fluoro-4-nitro-phenol and 1.72 g (10.0 mmol) of (2-chloro-ethyl)-diethyl-amine-hydrochloride obtained.

25 Yield: 1.65 g (86 % of theory)

$C_{12}H_{17}FN_2O_3$ ($M= 256.27$)

Calc.: molpeak($M+H$)⁺: 257

Found: molpeak ($M+H$)⁺: 257

R_f value: 0.1 (silica gel, EtOAc)

Z8b) 4-(2-diethylamino-ethoxy)-3-fluoro-phenylamine

The product was obtained analogously to intermediate product Z6b starting from

5 0.68 g (2.65 mmol) of diethyl-[2-(2-fluoro-4-nitro-phenoxy)-ethyl]-amine.

Yield: 0.60 g (quantitative yield)

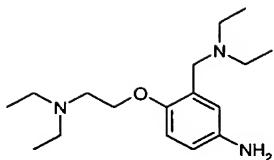
C₁₂H₁₉FN₂O (M= 226.29)

Calc.: molpeak(M+H)⁺: 227

Found: molpeak (M+H)⁺: 227

10 R_f value: 0.1 (silica gel, dichloromethane / MeOH 9:1)

Intermediate product 9:



Z9a) tert.butyl (3-diethylaminomethyl-4-hydroxy-phenyl)-carbaminate

At 80 °C a solution of 0.90 g (4.11 mmol) of Boc-anhydride in 20 mL THF was

5 added to a solution of 1.00 g (3.74 mmol) of 4-amino-2-diethylaminomethyl-phenol and 0.52 mL (3.74 mmol) of triethylamine in 20 mL abs. THF and the mixture was refluxed for 24 hours. 100 ml of 2 M aqueous sodium carbonate solution was added and the mixture was exhaustively extracted with ether. The combined org. extracts were dried over magnesium sulphate, evaporated down i. vac. and the residue was purified by column chromatography (silica gel, EtOAc).

10 Yield: 1.03 g (94 % of theory)

C₁₆H₂₆N₂O₃ (M= 294.39)

Calc.: molpeak(M+H)⁺: 295

Found: molpeak (M+H)⁺: 295

15 R_f value: 0.3 (silica gel, EtOAc)

Z9b) tert.butyl [4-(2-diethylamino-ethoxy)-3-diethylaminomethyl-phenyl]-carbaminate

The product was obtained analogously to intermediate product Z5a starting from

20 2.21 g (7.5 mmol) of tert.butyl (3-diethylaminomethyl-4-hydroxy-phenyl)-carbaminate and 1.72 g (10.0 mmol) of (2-chloro-ethyl)-diethyl-amine-hydrochloride.

Yield: 0.88 g (30 % of theory)

C₂₂H₃₉N₃O₃ (M= 393.56)

25 Calc.: molpeak(M+H)⁺: 394

Found: molpeak (M+H)⁺: 394

R_f value: 0.05 (silica gel, dichloromethane / MeOH 9:1)

Z9c) 4-(2-diethylamino-ethoxy)-3-diethylaminomethyl-phenylamine

5 mL TFA was added to a solution of 0.18 g (0.457 mmol) of tert.butyl [4-(2-diethylamino-ethoxy)-3-diethylaminomethyl-phenyl]-carbaminate in 5 mL

5 chloroform and the mixture was stirred for 1 hour at RT. 100 ml of 2 M aqueous sodium carbonate solution was added and exhaustively extracted with ether. The combined org. extracts were dried over magnesium sulphate and evaporated down i. vac.

Yield: 0.13 g (97 % of theory)

10 $C_{17}H_{31}N_3O$ ($M= 293.45$)

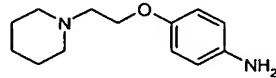
Calc.: molpeak($M+H$)⁺: 294

Found: molpeak ($M+H$)⁺: 294

R_f value: 0.05 (silica gel, dichloromethane / MeOH 4:1)

15

Intermediate product 10:



Z10) 4-(2-piperidin-1-yl-ethoxy)-phenylamine

15.4 g (111.00 mmol) of potassium carbonate was added to a solution of 4.0 g

20 (27.86 mmol) of 4-amino-2-chlorophenol and 5.1 g (27.86 mmol) of 1-(2-chloroethyl)-piperidine in 50 mL acetonitrile and the mixture was stirred for 48 hours at RT. The solvent was evaporated off i. vac., the residue was combined with water and the aqueous phase was exhaustively extracted with EtOAc. The combined org. extracts were washed with water, dried over magnesium sulphate, evaporated down i. vac. and the residue was purified by column chromatography (silica gel, dichloromethane / MeOH / conc. aqueous ammonia 90:10:1).

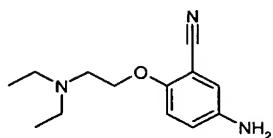
25 Yield: 77 mg (61 % of theory)

$C_{13}H_{19}ClN_2O$ ($M= 254.762$)

Calc.: molpeak($M+H$)⁺: 255/257

Found: molpeak (M+H)⁺: 255/257 (Cl)

Intermediate product 11:



5

Z11a) 2-hydroxy-5-nitro-benzonitrile

At 45-50 °C a solution of 36.0 mL of 65% aqueous nitric acid in 50 mL conc. acetic acid was added dropwise to a solution of 50 g (0.416 mol) of 2-hydroxy-

benzonitrile in 150 mL conc. acetic acid and the mixture was stirred for 1 hour at

10 50 °C. The reaction mixture was cooled to RT, diluted with 400 mL water and the precipitate formed was filtered off (mixture of o- and p-substituted product). The mother liquor was diluted with 1 L ice water and the precipitate formed was filtered off (product). The product mixture was dissolved in dichloromethane / MeOH and purified by column chromatography (silica gel, gradient dichloromethane / MeOH 10:0 → 4:1).

Yield: 25.22 g (37 % of theory)

C₇H₄N₂O₃ (M= 164.122)

Calc.: molpeak(M-H)⁻: 163

Found: molpeak (M-H)⁻: 163

20 R_f value: 0.35 (silica gel, dichloromethane / MeOH 9:1)

Z11b) 5-amino-2-hydroxy-benzonitrile

4.50 g (27.00 mmol) of 2-hydroxy-5-nitro-benzonitrile was added to a suspension of 0.45 g Pd/C (10 %) in 45 mL EtOAc and the mixture was hydrogenated for 1.5

25 hours under 3 bar H₂ atmosphere. The catalyst was filtered off and the residue dried i. vac.

Yield: 3.40 g (94 % of theory)

$C_7H_6N_2O$ ($M= 134.139$)

Calc.: molpeak($M-H$) $^+$: 133

Found: molpeak ($M-H$) $^+$: 133

R_f value: 0.3 (silica gel, dichloromethane / MeOH 9:1)

5

Z11c) 5-amino-2-(2-diethylamino-ethoxy)-benzonitrile

11.06 g (0.080 mol) of potassium carbonate was added to a solution of 2.683 g

(0.020 mol) of 5-amino-2-hydroxy-benzonitrile and 3.786 g (0.022 mol) of N,N-diethylamino-ethylchloride-hydrochloride in 100 mL abs. acetonitrile and the

10 mixture was stirred for 48 hours at RT. The solvent was evaporated off i. vac. and the residue was combined with water. The aqueous phase was exhaustively extracted with EtOAc, the combined org. extracts were washed with water, dried over magnesium sulphate and evaporated down i. vac. The residue was purified by column chromatography (silica gel, dichloromethane / MeOH / conc. aqueous
15 ammonia 90:10:1).

Yield: 0.80 g (17 % of theory)

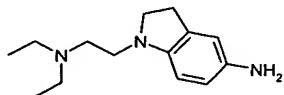
$C_{13}H_{19}N_3O$ ($M= 233.316$)

Calc.: molpeak($M+H$) $^+$: 234

Found: molpeak ($M+H$) $^+$: 234

20 R_f value: 0.15 (silica gel, dichloromethane / MeOH / conc. aqueous ammonia 90:10:1)

Intermediate product 12:



25 Z12a) diethyl-[2-(5-nitro-2,3-dihydro-indol-1-yl)-ethyl]-amine

1.00 g (7.262 mmol) of potassium carbonate was added to a solution of 0.477 g

(2.905 mmol) of 5-nitro-2,3-dihydro-1H-indole and 0.500 g (2.905 mmol) of N,N-diethylamino-ethylchloride-hydrochloride in 5 mL DMF and the mixture was stirred

for 16 hours at 90 °C. The reaction mixture was diluted with water and exhaustively extracted with EtOAc. The combined org. phases were dried over magnesium sulphate and evaporated down i. vac. The residue was purified by column chromatography (silica gel, EtOAc).

5 Yield: 0.14 g (18 % of theory)

$C_{14}H_{21}N_3O_2$ ($M= 263.342$)

Calc.: molpeak($M+H$) $^+$: 264

Found: molpeak ($M+H$) $^+$: 264

R_f value: 0.26 (silica gel, EtOAc / MeOH 9:1)

10

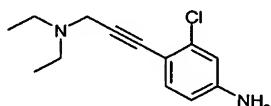
Z12b) 1-(2-diethylamino-ethyl)-2,3-dihydro-1H-indol-5-ylamine

140 mg (0.532 mmol) of diethyl-[2-(5-nitro-2,3-dihydro-indol-1-yl)-ethyl]-amine was added to a suspension of 50 mg of Raney-Ni in 5 mL MeOH and the mixture was hydrogenated for 1 hour at RT under 20 psi of H_2 atmosphere. The catalyst was

15 filtered off and the filtrate evaporated down i. vac. The crude product was reacted immediately without any further purification (cf. Example 12).

Yield: 80 mg (64 % of theory)

20 Intermediate product 13:



Z13a) [3-(2-chloro-4-nitro-phenyl)-prop-2-ynyl]-diethyl-amine

Under a nitrogen atmosphere 12.5 mL (0.090 mol) of 3-N,N-diethylamino-propyne was added to 25.00 g (0.106 mol) of 4-bromo-3-chloro-nitrobenzene, 43.7 mL

25 (0.315 mol) of triethylamine, 10.40 g (0.009 mol) of tetrakis[triphenylphosphine]-palladium(II) and 1.71 g (0.009 mol) of copper(I)-iodide in 250 mL acetonitrile and the mixture was refluxed for 18 hours. The reaction mixture was evaporated down i. vac., combined with EtOAc and the organic phase was washed with water. The

org. phase was evaporated down i. vac. and the residue was purified by column chromatography (silica gel, petroleum ether / EtOAc 10:0 → 4:1) followed by column chromatography (silica gel, dichloromethane).

Yield: 15.0 g (62 % of theory)

5 C₁₃H₁₅CIN₂O₂ (M= 266.730)

Calc.: molpeak(M+H)⁺: 267/269

Found: molpeak (M+H)⁺: 267/269 (Cl)

Z13b) 3-chloro-4-(3-diethylamino-prop-1-ynyl)-phenylamine

10 A solution of 15 mL of conc. aqueous HCl in 15 mL EtOH was added to a suspension of 4.189 g (75.00 mmol) of iron powder and 2.00 g (7.50 mmol) of [3-(2-chloro-4-nitro-phenyl)-prop-2-ynyl]-diethyl-amine in 20 mL of EtOH with vigorous stirring and the mixture was stirred for 30 minutes. The reaction mixture was neutralised with 200 mL of 10 % aqueous sodium carbonate solution and 15 exhaustively extracted with EtOAc. The combined org. phases were dried over magnesium sulphate, evaporated down i. vac. and the residue was purified by column chromatography (silica gel, gradient dichloromethane / 10 % conc. aqueous ammonia in MeOH 100:0 → 5:95).

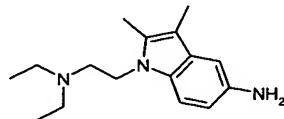
Yield: 0.45 g (25 % of theory)

20 C₁₃H₁₇CIN₂ (M= 236.747)

Calc.: molpeak(M+H)⁺: 237/239

Found: molpeak (M+H)⁺: 237/239 (Cl)

25 Intermediate product 14:



Z14a) [2-(2,3-dimethyl-5-nitro-indol-1-yl)-ethyl]-diethyl-amine

1.00 g (7.262 mmol) of potassium carbonate was added to a solution of 0.553 g (2.905 mmol) of 2,3-dimethyl-5-nitro-1H-indole and 0.500 g (2.905 mmol) of N,N-diethylamino-ethylchloride-hydrochloride in 5 mL DMF and the mixture was stirred for 16 hours at 90 °C. The reaction mixture was diluted with water and

5 exhaustively extracted with EtOAc. The combined org. phases were dried over magnesium sulphate and evaporated down i. vac. The residue was purified by column chromatography (silica gel, EtOAc / MeOH 9:1).

Yield: 0.15 g (18 % of theory)

$C_{16}H_{23}N_3O_2$ ($M= 289.3812$)

10 Calc.: molpeak($M+H$)⁺: 290

Found: molpeak ($M+H$)⁺: 290

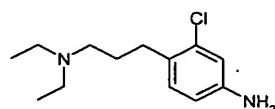
R_f value: 0.54 (silica gel, EtOAc / MeOH 9:1)

Z14b) 1-(2-diethylamino-ethyl)-2,3-dimethyl-1H-indol-5-ylamine

15 150 mg (0.518 mmol) of [2-(2,3-dimethyl-5-nitro-indol-1-yl)-ethyl]-diethyl-amine was added to a suspension of 100 mg of Raney-Ni in 5 mL MeOH and the mixture was hydrogenated for 1 hour at RT under 20 psi H₂ atmosphere. The catalyst was filtered off and the filtrate evaporated down i. vac. The crude product was reacted immediately without further purification (see Example 5).

20 Yield: 100 mg (74 % of theory)

Intermediate product 15:



Z15) 3-chloro-4-(3-diethylamino-propyl)-phenylamine

25 2.00 g (7.498 mmol) of 3-chloro-4-(3-diethylamino-prop-1-ynyl)-phenylamine (intermediate product Z13b) was added to a suspension of 0.50 g Raney-Ni in 50 mL abs. MeOH and the mixture was hydrogenated for 2.5 hours at RT and 50 psi H₂ atmosphere. The catalyst was filtered off, the filtrate evaporated down i. vac.

and the residue was purified by column chromatography (silica gel, gradient dichloromethane / 10 % conc. aqueous ammonia in MeOH 100:0 → 5:95).

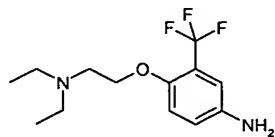
Yield: 0.90 g (50 % of theory)

$C_{13}H_{21}ClN$ ($M= 240.779$)

5 Calc.: molpeak($M+H$)⁺: 241/243

Found: molpeak ($M+H$)⁺: 241/243 (Cl)

Intermediate product 16:



10 Z16a) diethyl-[2-(4-nitro-2-trifluoromethyl-phenoxy)-ethyl]-amine

5.60 g (40.00 mmol) of potassium carbonate was added to a solution of 4.10 g (20.00 mmol) of 4-nitro-2-trifluoromethyl-phenol (J. Org. Chem. 1962, 27, 4660-4662.) in 40 mL DMF and the mixture was heated to 80 °C. A solution of 3.5 g (20.00 mmol) of N,N-diethylamino-ethylchloride-hydrochloride in 10 mL DMF was added dropwise and the mixture was stirred for a further 3 hours at 80 °C. The reaction mixture was diluted with 100 mL sat. aqueous NaCl solution and exhaustively extracted with EtOAc. The combined org. extracts were washed with 10 % aqueous sodium carbonate solution, dried over magnesium sulphate and evaporated down i. vac.

15 Yield: 7.5 g (80 % of theory)

$C_{13}H_{17}F_3N_2O_3$ ($M= 306.287$)

Calc.: molpeak($M+H$)⁺: 307

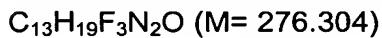
Found: molpeak ($M+H$)⁺: 307

20 Z16b) 4-(2-diethylamino-ethoxy)-3-trifluoromethyl-phenylamine

7.0 g (22.854 mmol) of 4-(2-diethylamino-ethoxy)-3-trifluoromethyl-phenylamine was added to a suspension of 0.50 g Pd/C (10 %) in EtOAc and the mixture was

hydrogenated for 6 hours at 50 °C and 50 psi H₂ atmosphere. The catalyst was filtered off and the filtrate evaporated down i. vac. MTBE was added and the org. phase was washed several times with water, dried over magnesium sulphate, filtered through activated charcoal and evaporated down i. vac.

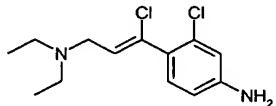
5 Yield: 4.40 g (70 % of theory)



Calc.: molpeak(M+H)⁺: 277

Found: molpeak (M+H)⁺: 277

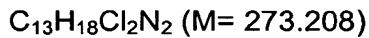
10 Intermediate product 17:



Z17) 3-chloro-4-((Z)-1-chloro-3-diethylamino-propenyl)-phenylamine

A solution of 15 mL conc. aqueous HCl in 15 mL EtOH was added to a suspension of 2.20 g (75.00 mmol) of iron powder and 2.20 g (8.25 mmol) of [3-(2-chloro-4-nitro-phenyl)-prop-2-ynyl]-diethyl-amine (intermediate product Z13a) in 20 mL EtOH with vigorous stirring and the mixture was stirred for 2 hours at 80 °C. The reaction mixture was neutralised with 200 mL 10 % aqueous sodium carbonate solution and exhaustively extracted with EtOAc. The combined org. phases were dried over magnesium sulphate and evaporated down i. vac.

15 20 Yield: 1.70 g (75 % of theory)



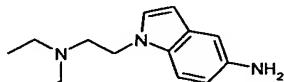
Calc.: molpeak(M+H)⁺: 273/275/277

Found: molpeak (M+H)⁺: 273/275/277 (Cl₂)

R_f value: 0.71 (silica gel, EtOAc / MeOH / conc. aqueous ammonia 90:10:1)

25

Intermediate product 18:



Z18a) diethyl-[2-(5-nitro-indol-1-yl)-ethyl]-amine

1.00 g (7.262 mmol) of potassium carbonate was added to a solution of 0.47 g (2.905 mmol) of 5-nitro-1H-indole and 0.50 g (2.905 mmol) of N,N-diethylamino-ethylchloride-hydrochloride in 5 mL DMF and the mixture was stirred for 3 hours at 80 °C. The reaction mixture was diluted with water and exhaustively extracted with EtOAc. The combined org. phases were dried over magnesium sulphate and evaporated down i. vac.

Yield: 0.65g (86 % of theory)

10 C₁₄H₁₉N₃O₂ (M= 261.326)

Calc.: molpeak(M+H)⁺: 262

Found: molpeak (M+H)⁺: 264

Z18b) 1-(2-diethylamino-ethyl)-1H-indol-5-ylamine

15 650 mg (2.487 mmol) of diethyl-[2-(5-nitro-indol-1-yl)-ethyl]-amine was added to a suspension of 200 mg Raney-Ni in 10 mL MeOH and the mixture was hydrogenated for 2 hours at RT under 20 psi H₂ atmosphere. The catalyst was filtered off and the filtrate evaporated down i. vac.

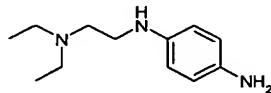
Yield: 520 mg (90 % of theory)

20 C₁₄H₂₁N₃ (M= 231.344)

Calc.: molpeak(M+H)⁺: 232

Found: molpeak (M+H)⁺: 232

Intermediate product 19:



25

Z19a) N'-(2-chloro-4-nitro-phenyl)-N,N-diethyl-ethane-1,2-diamine

25 mL of 50 % aqueous KOH solution was added to a solution of 1.00 g (5.795 mmol) of 2-chloro-4-nitro-phenylamine, 2.995 g (17.384 mmol) of (2-chloro-ethyl)-

diethyl-amine and 0.66 g (2.898 mmol) of TEBAC in 50 mL toluene and the mixture was refluxed for 5 days. The reaction mixture was cooled to RT and exhaustively extracted with EtOAc. The combined org. phases were dried over magnesium sulphate, evaporated down i. vac. and the residue was purified by 5 column chromatography (silica gel, dichloromethane / MeOH 4:1).

Yield: 1.2 g (76 % of theory)

$C_{12}H_{18}ClN_3O_2$ ($M= 271.749$)

Calc.: molpeak($M+H$)⁺: 272/274

Found: molpeak ($M+H$)⁺: 272/274 (Cl)

10

Z19b) N-(2-diethylamino-ethyl)-benzene-1,4-diamine

1.20 mg (4.416 mmol) of N'-(2-chloro-4-nitro-phenyl)-N,N-diethyl-ethane-1,2-diamine was added to a suspension of 200 mg Raney-Ni in 20 mL MeOH and the mixture was hydrogenated for 2 hours at RT under 20 psi H₂ atmosphere. The catalyst was filtered off and the filtrate evaporated down i. vac.

15 Yield: 800 mg (87 % of theory)

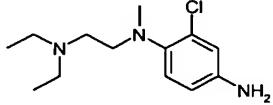
$C_{12}H_{21}N_3$ ($M= 207.321$)

Calc.: molpeak($M+H$)⁺: 207

Found: molpeak ($M+H$)⁺: 207

20

Intermediate product 20:



Z20a) N-(2-chloro-4-nitro-phenyl)-N',N'-diethyl-N-methyl-ethane-1,2-diamine

1.00 mL (6.181 mmol) of N,N-diethyl-N'-methyl-ethane-1,2-diamine was added to

25 a solution of 1.085 g (6.181 mmol) of 2-chloro-1-fluoro-4-nitrobenzene and 1.03 mL (7.417 mmol) of triethylamine in 20 mL THF and the mixture was stirred for 48 hours at RT. The reaction mixture was combined with sat. aqueous sodium

bicarbonate solution and exhaustively extracted with EtOAc. The combined org. extracts were dried over magnesium sulphate and evaporated down i. vac.

Yield: 1.60 mg (91 % of theory)

$C_{13}H_{20}ClN_3O_2$ ($M= 285.776$)

5 Calc.: molpeak($M+H$)⁺: 286/288

Found: molpeak ($M+H$)⁺: 286/288 (Cl)

Z20b) 2-chloro-N'-(2-diethylamino-ethyl)-N'-methyl-benzene-1,4-diamine

1.60 mg (5.599 mmol) of N-(2-chloro-4-nitro-phenyl)-N',N'-diethyl-N-methyl-

10 ethane-1,2-diamine was added to a suspension of 200 mg Raney-Ni in 20 mL MeOH and the mixture was hydrogenated for 2 hours at RT under 20 psi H₂ atmosphere. The catalyst was filtered off and the filtrate evaporated down i. vac.

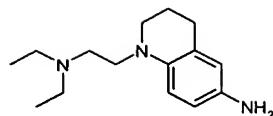
Yield: 1.30 mg (91 % of theory)

$C_{13}H_{22}ClN_3$ ($M= 255.793$)

15 Calc.: molpeak($M+H$)⁺: 256/258

Found: molpeak ($M+H$)⁺: 256/258

Intermediate product 21:



Z21a) N-[1-(2-diethylamino-ethyl)-1,2,3,4-tetrahydro-quinolin-6-yl]-2,2,2-trifluoro-acetamide

5 50 mL of 50 % aqueous KOH solution was added to a solution of 3.00 g (12.284 mmol) of 6-nitro-1,2,3,4-tetrahydro-quinoline, 6.342 g (36.852 mmol) of (2-chloro-ethyl)-diethyl-amine and 1.68 g (7.370 mmol) of TEBAC in 100 mL toluene and the mixture was stirred for 1 hour at 80 °C. The reaction mixture was cooled to RT and exhaustively extracted with EtOAc. The combined org. phases were dried over
 10 magnesium sulphate, evaporated down i. vac. and the residue was purified by column chromatography (silica gel, EtOAc / MeOH 9:1).

Yield: 0.75 g (18 % of theory)

C₁₇H₂₄F₃N₃O (M= 343.396)

Calc.: molpeak(M+H)⁺: 344

15 Found: molpeak (M+H)⁺: 344

Z21b) 1-(2-diethylamino-ethyl)-1,2,3,4-tetrahydro-quinolin-6-ylamine

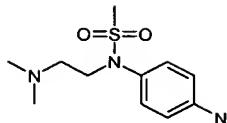
1.1 mL 6 M aqueous NaOH solution was added to a solution of 0.75 g (2.184 mmol) of N-[1-(2-diethylamino-ethyl)-1,2,3,4-tetrahydro-quinolin-6-yl]-2,2,2-trifluoro-acetamide in 5 mL MeOH at 0 °C and the mixture was stirred for 15 minutes at 0 °C and for 1 hour at RT. The reaction mixture was evaporated down i. vac., sat. aqueous sodium bicarbonate solution was added and the mixture was exhaustively extracted with EtOAc. The combined org. extracts were dried over magnesium sulphate, evaporated down i. vac. and the residue was purified by column chromatography (silica gel, dichloromethane / MeOH / conc. aqueous ammonia 90:10:1).

Yield: 220 mg (41 % of theory)

C₁₅H₂₅N₃ (M= 247.387)

Calc.: molpeak(M+H)⁺: 248
 Found: molpeak (M+H)⁺: 248

5 Intermediate product 22:



Z22a) N-(4-nitro-phenyl)-methanesulphonic acid amide

27.60 g (0.20 mol) of 4-nitroaniline was dissolved in 100 mL pyridine. At 0°C 16.3 mL (0.21 mol) of methanesulphonic acid chloride were added dropwise so that the reaction temperature did not exceed 20-25°C. Then the mixture was stirred for 2.5 hours at RT. The reaction mixture was added to 800 mL ice water with stirring and stirred for 30 minutes. The precipitated solid was filtered off, washed with 500 mL water and 100 mL EtOH and dried.

Yield: 41.00 g (95 % of theory)

15 melting point: 183-184°C

R_f value: 0.50 (silica gel, dichloromethane / EtOAc = 90:10)

Z22b) N-(2-dimethylamino-ethyl)-N-(4-nitro-phenyl)-methanesulphonic acid amide

36.00 g (0.166 mol) of N-(4-nitro-phenyl)-methanesulphonic acid amide was dissolved in 2000 mL acetone. The solution was combined with 47.8 g (0.332 mol) of 1-chloro-2-dimethylaminoethane * HCl, 68.8 g (0.498 mol) of potassium carbonate, 5.0 g (0.033 mol) of sodium iodide and 50 mL water. It was refluxed for 16 hours with stirring. After the addition of another 23.9 g (0.166 mol) of 1-chloro-2-dimethylaminoethane * HCl, 45.9 g (0.332 mol) of potassium carbonate and 5.0 g (0.033 mol) of sodiumiodide, the mixture was refluxed for 5 hours with stirring. At RT the inorganic salts were filtered off. The filtrate was evaporated down i. vac. and the residue dissolved in EtOAc. The org. phase was washed 2x with semisat.

aqueous sodium chloride solution, dried over magnesium sulphate, filtered and evaporated down i. vac.

Yield: 30.57 g (64 % of theory)

C₁₁H₁₇N₃O₄S (M= 287.340)

5 Calc.: molpeak(M+H)⁺: 288

Found: molpeak (M+H)⁺: 288

R_f value: 0.60 (silica gel, dichloromethane / MeOH / conc. aqueous ammonia = 90:10:1)

10 Z22c) N-(4-amino-phenyl)-N-(2-dimethylamino-ethyl)-methanesulphonic acid amide

9.00 g (31.3 mmol) of N-(2-dimethylamino-ethyl)-N-(4-nitro-phenyl)-methanesulphonic acid amide were dissolved in 120 mL MeOH. After the addition of 1.0 g of 10% palladium/charcoal the mixture was hydrogenated for 1 hour at RT and 50 psi H₂ atmosphere. The reaction mixture was filtered and the filtrate evaporated down i. vac. The residue was stirred with ether/petroleum ether = 1:1. The solid was filtered off, washed with ether/petroleum ether = 1:1 and dried.

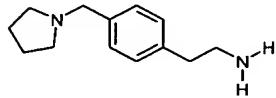
Yield: 7.65 g (95 % of theory)

melting point: 151-152°C

20 R_f value: 0.40 (silica gel, dichloromethane / MeOH / conc. aqueous ammonia = 90:10:1)

Intermediate product 23:

25

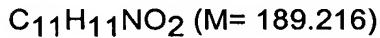


Z23a) ethyl 4-cyanomethyl-benzoate

A solution of 500 g (2.057 mol) of ethyl 4-bromomethyl-benzoate in 1000 ml of ethanol is added dropwise to a solution of 147.5 g (2.263 mol) of potassium cyanide in 250 mL of hot water. The reaction mixture is refluxed for one hour and stirred for 12 hours at RT. A further 73.7 g (0.5 mol) of potassium cyanide are

5 added and the mixture is refluxed for two hours. The solid present in the reaction mixture is filtered off and the filtrate is filtered through a mixture of silica gel and activated charcoal. The filtrate obtained is evaporated down and the residue is poured onto 1000 mL of water. The aqueous solution is extracted with MTBE and the organic phase is extracted three times with water. Then the organic phase is
 10 dried over magnesium sulphate and the solvent is distilled off using the rotary evaporator. The product is purified by column chromatography on silica gel (petroleum ether/ ethyl acetate 8:2).

Yield: 164.46 g (42.2 % of theory)



15 Calc.: molpeak $(\text{M}+\text{H})^+$: 190

Found: molpeak $(\text{M}+\text{H})^+$: 190

R_f value: 0.3 (silica gel, petroleum ether/EtOAc 8:2)

Z23b) 4-cyanomethyl-benzoic acid

20 A solution of 10 g (53 mol) of ethyl 4-cyanomethyl-benzoate and 2.02 mL of a 1 M sodium hydroxide solution in 100 mL of ethanol is refluxed for one hour. Then the reaction solution is evaporated down and the residue is combined with ice water. Concentrated hydrochloric acid is added dropwise to the reaction solution until no more precipitate is formed. The precipitate is filtered off, washed twice with water
 25 and dried.

Yield: 4.7 g (55 % of theory)



Calc.: molpeak $(\text{M}-\text{H})^-$: 160

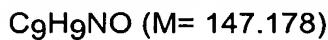
Found: molpeak $(\text{M}-\text{H})^-$: 160

Z23c) (4-hydroxymethyl-phenyl)-acetonitrile

5.17 g (32 mol) of CDI are added to a solution of 4.7 g (29 mol) of 4-cyanomethylbenzoic acid in 250 mL of tetrahydrofuran and stirred until no more gas is given off. This reaction mixture is added dropwise to a solution of 3.29 g (87 mol) of

5 sodium borohydride in 200 mL of water in such a way that the temperature does not exceed 30°C. The mixture is stirred for two hours and the reaction mixture is adjusted to pH 3-4 with potassium hydrogen sulphate solution. Then it is extracted with EtOAc, the organic phase is dried over magnesium sulphate and the solvent is separated off using the rotary evaporator.

10 Yield: 2.6 g (60.9 % of theory)



Calc.: molpeak(M-H)⁻: 146

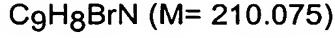
Found: molpeak (M-H)⁻: 146

15 Z23d) (4-bromomethyl-phenyl)-acetonitrile

0.86 mL (9 mmol) of phosphorus tribromide are added dropwise to a solution of 2.6 g (17.66 mmol) of (4-hydroxymethyl-phenyl)-acetonitrile in 25 mL MTBE at 0°C. After the reaction has ended the reaction mixture is combined with water at RT, the organic phase is separated off and these are extracted successively with

20 sodium hydrogen carbonate solution and water. The organic phase is dried over magnesium sulphate and the solvent is distilled off using the rotary evaporator.

Yield: 2.9 g (78.1 % of theory)



Calc.: molpeak(M+H)⁺: 209/211

25 Found: molpeak (M+H)⁺: 209/211

Z23e) (4-pyrrolidin-1-ylmethyl-phenyl)-acetonitrile

0.446 mL (5.44 mmol) of pyrrolidine and 1.366 g (9.882 mmol) of potassium

carbonate are added to 20 mL of dimethylformamide. 1.038 g (4.941 mmol) of (4-

30 bromomethyl-phenyl)-acetonitrile are added with stirring and the mixture is stirred

for 12 hours at RT. The reaction mixture is evaporated down in the rotary evaporator and the residue is extracted with EtOAc and water. The organic phase is dried over magnesium sulphate and the solvent is removed using the rotary evaporator.

5 Yield: 0.732 g (74 % of theory)

$C_{13}H_{16}N_2$ ($M= 200.286$)

Calc.: molpeak($M+H$) $^+$: 201

Found: molpeak ($M+H$) $^+$: 201

R_f value: 0.5 (silica gel, dichloromethane / MeOH / conc. aqueous ammonia

10 90:10:1)

Z23f) 2-(4-pyrrolidin-1-ylmethyl-phenyl)-ethylamine

A reaction mixture of 0.73 g (3.66 mmol) of (4-pyrrolidin-1-ylmethyl-phenyl)-acetonitrile and 0.1 g Raney nickel in 25 mL of methanolic ammonia solution is

15 hydrogenated for 9 hours at 50°C under 3 bar hydrogen.

Yield: 0.72 g (96.4 % of theory)

$C_{13}H_{20}N_2$ ($M= 204.31$)

Calc.: molpeak($M+H$) $^+$: 205

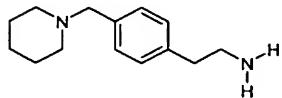
Found: molpeak ($M+H$) $^+$: 205

20 R_f value: 0.23 (silica gel, dichloromethane / MeOH / conc. aqueous ammonia

90:10:1)

Intermediate product 24

25



Z24a) (4-piperidin-1-ylmethyl-phenyl)-acetonitrile

Prepared analogously to Example Z23e from piperidine and (4-bromomethyl-phenyl)-acetonitrile.

Yield: 1.6 g (39 % of theory)

C₁₄H₁₈N₂(M= 214.31)

5 Calc.: molpeak(M+H)⁺: 215

Found: molpeak (M+H)⁺: 215

R_f value: 0.4 (silica gel, cyclohexane/EtOAc 1:1)

10 Z24b) 2-(4-piperidin-1-ylmethyl-phenyl)-ethylamine

Prepared analogously to Example Z23f from (4-piperidin-1-ylmethyl-phenyl)-acetonitrile

Yield: 1.4 g (85.9 % of theory)

C₁₄H₂₂N₂ (M= 218.34)

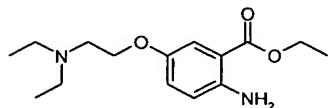
15 Calc.: molpeak(M+H)⁺: 219

Found: molpeak (M+H)⁺: 219

R_f value: 0.2 (silica gel, dichloromethane/ethanol/ammonia 20:1:0.1)

Intermediate product 25:

20



Z25a) Ethyl 5-hydroxy-2-nitrobenzoate

A solution of 5.00 g (27.304 mmol) 5-hydroxy-2-nitrobenzoic acid was refluxed in 25 200 mL ethanolic HCl for 5 h and then stirred for 48 h at RT. The reaction mixture was evaporated down i. vac. and diluted with EtOAc. The org. phase was washed with water, dried over magnesium sulphate and evaporated down i. vac.. The crude product was used in the next reaction step without any further purification.

Yield: 5.00 g (87% of theory)

C₉H₉NO₅ (M= 211,176)

Calc.: molpeak (M-H)⁻: 210

Found: molpeak (M-H)⁻: 210

5

Z25b) Ethyl 2-nitro-5-(2-diethylamino-ethoxy)-benzoate

Prepared analogously to intermediate product Z5a from ethyl 5-hydroxy-2-nitrobenzoate and (2-chloroethyl)-diethyl-amine-hydrochloride

Yield: 6.30 g (85% of theory)

10 C₁₅H₂₂N₂O₅ (M= 310,353)

Calc.: molpeak (M+H)⁺: 311

Found: molpeak (M+H)⁺: 311

15 Z25c) ethyl 2-amino-5-(2-diethylamino-ethoxy)-benzoate

Prepared analogously to intermediate product Z5b from ethyl 2-nitro-5-(2-diethylamino-ethoxy)-benzoate. Column chromatography (silica gel, EtOAc/MeOH/ammonia 90:10:1) yielded the product.

Yield: 4.00 g (71% of theory)

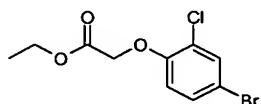
20 C₁₅H₂₄N₂O₃ (M= 280,370)

Calc.: molpeak (M+H)⁺: 281

Found: molpeak (M+H)⁺: 281

Intermediate product 26: ethyl (4-bromo-2-chloro-phenoxy)-acetate

25



Z26) 14.5 mL (83.242 mmol) Hünig base was added to a solution of 7.800 g (37.222 mmol) 4-bromo-2-chlorophenol and 4.70 mL (41.537 mmol) ethyl bromoacetate in 100 mL DMF and the mixture was stirred for 4 h at 100 °C. The reaction mixture was combined with water and exhaustively extracted with EtOAc.

5 The combined org. phases were washed with saturated aqueous sodium bicarbonate, water and saturated aqueous NaCl, dried over sodium sulphate and evaporated down i. vac. . The crude product was used in the next reaction step without any further purification.

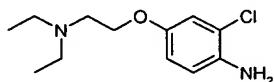
Yield: 11.36 g (quant. yield)

10 C₁₀H₁₀BrClO₃ (M= 293.546)

R_f value: 0.65 (silica gel, dichloromethane)

Intermediate product 27:

15



Z27a) [2-(3-chloro-4-nitro-phenoxy)-ethyl]-diethyl-amine

Prepared analogously to intermediate product Z5a starting from 3-chloro-4-nitro-phenol and (2-chloro-ethyl)-diethyl-amine.

20 Yield: 1.25 g (79% of theory)

C₁₂H₁₇ClN₂O₃ (M= 272.734)

Calc.: molpeak (M+H)⁺: 273/275

Found: molpeak (M+H)⁺: 273/275 (Cl)

R_f value: 0.44 (silica gel, dichloromethane / MeOH 9:1).

25

Z27b) 2-chloro-4-(2-diethylamino-ethoxy)-phenylamine

A suspension of 1.24 g (4.547 mmol) [2-(3-chloro-4-nitro-phenoxy)-ethyl]diethyl-amine (Z27a) and 300 mg Raney nickel in EtOAc was hydrogenated at RT and 3 bar. The catalyst was filtered off and the filtrate evaporated down i. vac. .

30 Yield: 1.10 g (quant. yield)

$C_{12}H_{19}ClN_2O$ ($M= 242.751$)

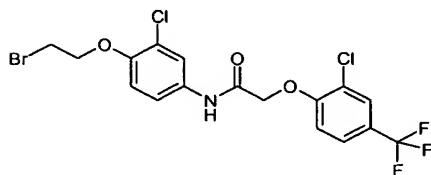
Calc.: molpeak ($M+H$) $^+$: 243/245

Found: molpeak ($M+H$) $^+$: 243/245 (Cl)

R_f value: 0.41 (silica gel, dichloromethane / MeOH 9:1).

5

Intermediate product 28:



10 Z28a) N-(3-chloro-4-hydroxy-phenyl)-2-(2-chloro-4-trifluoromethyl-phenoxy)-acetamide

17.31 mL (98.510 mmol) Hünig base was added at RT to a solution of 7.600 g (29.850 mmol) (2-chloro-4-trifluoromethyl-phenoxy)-acetic acid (Z2b), 4.370 g (29.850 mmol) 4-amino-2-chloro-phenol and 10.56 g (32.840 mmol) TBTU in 550

15 mL as. THF and the mixture was stirred for 48 h. The reaction mixture was evaporated down i. vac. and diluted with EtOAc. The org. phase was washed with water, saturated aqueous sodium bicarbonate and saturated aqueous NaCl, dried over sodium sulphate and evaporated down i. vac. Column chromatography (silica gel, gradient dichloromethane / MeOH 99:1 → 19:1) yielded the product.

20 Yield: 4.200 g (37% of theory)

$C_{15}H_{10}Cl_2F_3NO_3$ ($M= 380.153$)

Calc.: molpeak ($M+H$) $^+$: 380/382/384

Found: molpeak ($M+H$) $^+$: 380/382/384 (Cl₂)

R_f value: 0.58 (silica gel, dichloromethane / MeOH 19:1).

25

Z28b) N-[4-(2-bromo-ethoxy)-3-chloro-phenyl]-2-(2-chloro-4-trifluoromethyl-phenoxy)-acetamide

A solution of 3.66 mL (41.56 mmol) 1,2-dibromoethane in 5 mL DMF was slowly added at RT to a suspension of 1.580 g (4.156 mmol) N-(3-chloro-4-hydroxy-phenyl)-2-(2-chloro-4-trifluoromethyl-phenoxy)-acetamide and 2.880 g (8.310 mmol) potassium carbonate in 20 mL DMF and the mixture was stirred for 2.5 h.

5 The reaction mixture was evaporated down i. vac. and diluted with EtOAc. The org. phase was washed with water and saturated aqueous NaCl, dried over magnesium sulphate and evaporated down i. vac. Column chromatography (silica gel, petroleum ether → dichloromethane) yielded the product.

Yield: 1.120 g (55% of theory)

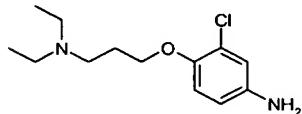
10 $C_{17}H_{13}BrCl_2F_3NO_3$ ($M= 487.103$)

Calc.: molpeak ($M+H$) $^+$: 486/488/490/492

Found: molpeak ($M+H$) $^+$: 486/488/490/492 ($BrCl_2$)

R_f value: 0.72 (silica gel, dichloromethane / MeOH 49:1).

15 Intermediate product 29:



Z29a) [2-(2-chloro-4-nitro-phenoxy)-propyl]-diethyl-amine

20 At 0 °C 1.60 g (33.000 mmol) NaH (50% in oil) was added to a solution of 5.30 g (30.000 mmol) 3-chloro-4-fluoro-nitrobenzene and 4.30 g (33.000 mmol) 3-diethylamino-propanol in 50 mL abs. DMF and the mixture was stirred for 2 h at 0 °C and for 1 h at RT. The reaction mixture was evaporated down i. vac. and diluted with EtOAc. The org. phase was washed with water, dried over sodium sulphate and evaporated down i. vac. Column chromatography (silica gel, dichloromethane / EtOH / conc. aqueous ammonia 90:10:0.1) yielded the product.

25 Yield: 8.00 g (93% of theory)

$C_{13}H_{19}ClN_2O_3$ ($M= 286.761$)

R_f value: 0.30 (silica gel, dichloromethane / MeOH / conc. aqueous ammonia 90:10:0.1).

Z29b) 3-chloro-4-(3-diethylamino-propoxy)-phenylamine

5 A suspension of 8.00 g (27.900 mmol) [2-(2-chloro-4-nitro-phenoxy)-propyl]-diethyl-amine (Z29a) and 0.80 g Raney nickel in 170 mL MeOH was hydrogenated for 8 h at RT and 50 psi. The catalyst was filtered off and the filtrate evaporated down i. vac. .

Yield: 6.70 g (93% of theory)

10 $C_{13}H_{21}ClN_2O$ ($M= 256.778$)

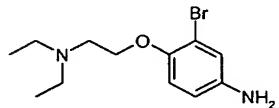
Calc.: molpeak ($M+H$) $^+$: 257/259

Found: molpeak ($M+H$) $^+$: 257/259 (Cl)

R_f value: 0.40 (silica gel, dichloromethane / MeOH / conc. aqueous ammonia 50:10:0.1).

15

Intermediate product 30:



20 Z30a) [2-(2-bromo-4-nitro-phenoxy)-ethyl]-diethyl-amine

Prepared analogously to Intermediate product Z29a starting from 2-bromo-1-fluoro-4-nitro-benzene and 2-diethylamino-ethanol.

Yield: 0.790 g (83% of theory)

$C_{12}H_{17}BrN_2O_3$ ($M= 317.185$)

25 Calc.: molpeak ($M+H$) $^+$: 317/319

Found: molpeak ($M+H$) $^+$: 317/319 (Br)

R_f value: 0.48 (silica gel, dichloromethane / MeOH 9:1).

Z30b) 3-bromo-4-(2-diethylamino-ethoxy)-phenylamine

Prepared analogously to Intermediate product Z29b starting from [2-(2-bromo-4-nitro-phenoxy)-ethyl]-diethyl-amine (Z30a).

Yield: 0.670 g (96% of theory)

$C_{12}H_{19}BrN_2O$ ($M= 287.202$)

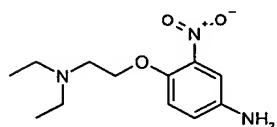
5 Calc.: molpeak ($M+H$) $^+$: 287/289

Found: molpeak ($M+H$) $^+$: 287/289 (Br)

R_f value: 0.30 (silica gel, dichloromethane / MeOH 9:1).

Intermediate product 31:

10



Z31a) N-[4-(2-diethylaminoethoxy)-3-nitrophenyl]-acetamide

0.737 g (7.286 mmol) potassium nitrate was added batchwise at -10 °C to a
15 solution of 1.520 g (6.072 mmol) N-[4-(2-diethylaminoethoxy)-phenyl]-acetamide in 25 mL conc. sulphuric acid and the mixture was stirred for 1 h at -10 °C. The reaction mixture was poured onto a mixture of ice and conc. aqueous ammonia and the aqueous phase was exhaustively extracted with EtOAc. The combined org. phases were dried over sodium sulphate and evaporated down i. vac. .

20 Yield: 1.8 g (quant. yield)

$C_{14}H_{21}N_3O_4$ ($M= 295.341$)

Calc.: molpeak ($M+H$) $^+$: 296

Found: molpeak ($M+H$) $^+$: 296

R_f value: 0.51 (Alox, dichloromethane / MeOH 39:1).

25

Z31b) 4-(2-diethylaminoethoxy)-3-nitro-phenylamine

A solution of 1.85 g (6.264 mmol) N-[4-(2-diethylaminoethoxy)-3-nitrophenyl]-acetamide (Z31a) in semiconc. aqueous HCl was stirred for 2 h at 100 °C, cooled

to RT, made basic with ice and conc. aqueous ammonia and the aqueous phase was exhaustively extracted with EtOAc. The combined org. phases were washed with water and dried over sodium sulphate.

Yield: 1.38 g (87% of theory)

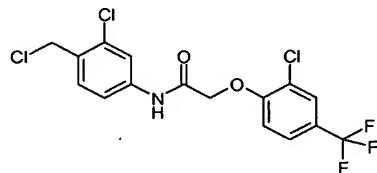
5 $C_{12}H_{19}N_3O_3$ ($M= 253.304$)

Calc.: molpeak $(M+H)^+$: 254

Found: molpeak $(M+H)^+$: 254

R_f value: 0.68 (Alox, dichloromethane / MeOH 39:1).

10 Intermediate product 32:



Z32a) N-(3-chloro-4-hydroxymethyl-phenyl)-2-(2-chloro-4-trifluoromethyl-

15 phenoxy)-acetamide

0.55 mL (4.200 mmol) of isopropyl chloroformate was slowly added dropwise at -5 °C to a solution of 1.018 g (4.000 mmol) of (2-chloro-4-trifluoromethyl-phenoxy)-acetic acid (Z2b) and 0.46 mL (4.200 mmol) N-methylmorpholine in 5 mL abs.

DMF and the mixture was stirred for another 5 min.. 0.662 g (4.200 mmol) (4-

20 amino-2-chloro-phenyl)-methanol was added at -5 °C, the mixture was stirred for 2 h at RT and then the reaction mixture was poured onto ice water. The precipitate was filtered off, washed with water and dried in HV.

Yield: 1.360 g (83% of theory)

$C_{16}H_{12}Cl_2F_3NO_3$ ($M= 394.180$)

25 R_f value: 0.50 (silica gel, dichloromethane / MeOH 19:1).

Z32b) N-(3-chloro-4-chloromethyl-phenyl)-2-(2-chloro-4-trifluoromethyl-phenoxy)-acetamide

1.12 mL (16.440 mmol) thionyl chloride was added to a solution of 1.620 g (4.110 mmol) N-(3-chloro-4-hydroxymethyl-phenyl)-2-(2-chloro-4-trifluoromethyl-phenoxy)-acetamide (Z32a) in 30 mL toluene and the mixture was stirred for 2 h at 80 °C. The reaction mixture was evaporated down i. vac. and the residue
 5 recrystallised from ether/petroleum ether. The precipitate was filtered off, washed with petroleum ether and dried in a HV.

Yield: 1.100 g (65% of theory)

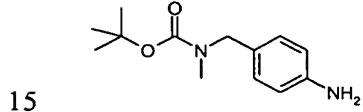
$C_{16}H_{11}Cl_3F_3NO_2$ ($M= 412.626$)

Calc.: molpeak ($M+H$)⁺: 412/414/416/418

10 Found: molpeak ($M+H$)⁺: 412/414/416/418 (Cl_3)

R_f value: 0.69 (silica gel, petroleum ether / EtOAc 3:1).

Intermediate product 33:



Z33a) tert-butyl methyl-(4-nitro-benzyl)-carbaminate

17.68 g (81.00 mmol) Boc-anhydride was slowly added at 0 °C to a solution of 13.40 g (81.00 mmol) methyl-(4-nitro-benzyl)-amine in 25 mL EtOAc and the
 20 mixture was stirred for 3 h at RT. The org. phase was washed with water, dried over sodium sulphate and evaporated down i. vac. .

Yield: 21.36 g (99% of theory)

$C_{13}H_{18}N_2O_4$ ($M= 266.299$)

R_f value: 0.60 (silica gel, petroleum ether / EtOAc 3:7).

25

Z33b) tert-butyl (4-amino-benzyl)-methyl-carbaminate

A suspension of 23.00 g (86.00 mmol) tert-butyl methyl-(4-nitro-benzyl)-carbaminate (Intermediate product Z33a) and 2.30 g Raney nickel in 460 mL EtOH/EtOAc (1:1) was hydrogenated at RT and 3 bar. The catalyst was filtered off,

the filtrate evaporated down i. vac. and the residue purified by column chromatography (silica gel, petroleum ether / EtOAc 1:1).

Yield: 9.23 g (45% of theory)

$C_{13}H_{20}N_2O_2$ ($M= 236.317$)

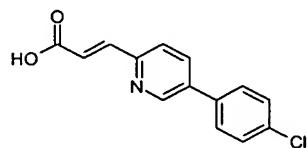
5 Calc.: molpeak ($M+H$) $^+$: 237

Found: molpeak ($M+H$) $^+$: 237

R_f value: 0.40 (silica gel, petroleum ether / EtOAc 1:1).

Intermediate product 34:

10



Z34a) ethyl (E)-3-[5-(4-chloro-phenyl)-pyridin-2-yl]-acrylate

2.000 g (5.560 mmol) (ethoxycarbonylmethylene)-triphenylphosphorane was

15 added at RT to a solution of 1.100 g (5.050 mmol) 5-(4-chloro-phenyl)-pyridine-2-carbaldehyde in 50 mL abs. THF and the mixture was stirred for 4 h at RT. The reaction mixture was evaporated down i. vac. and the residue purified by column chromatography (Alox, neutral, act. II-III, petroleum ether / EtOAc 5:1).

Recrystallisation from petroleum ether yielded the product.

20 Yield: 1.200 g (83% of theory)

$C_{16}H_{14}ClNO_2$ ($M= 287.748$)

Calc.: molpeak ($M+H$) $^+$: 288/290

Found: molpeak ($M+H$) $^+$: 288/290 (Cl)

R_f value: 0.60 (silica gel, petroleum ether / EtOAc 5:1).

25

Z34b) (E)-3-[5-(4-chloro-phenyl)-pyridin-2-yl]-acrylic acid

12.6 mL aqueous NaOH (1 M) was added at RT to a suspension of 1.200 g (4.200 mmol) ethyl (E)-3-[5-(4-chloro-phenyl)-pyridin-2-yl]-acrylate (Z34a) in 50 mL EtOH

and the mixture was stirred for 1 h . 12.6 mL aqueous HCl (1 M) was added at 0 °C. The precipitate formed was filtered off, washed with water and dried i. vac. at 100 °C.

Yield: 1.000 g (92% of theory)

5 C₁₄H₁₀CINO₂ (M= 259.694)

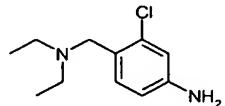
Calc.: molpeak (M+H)⁺: 260/262

Found: molpeak (M+H)⁺: 260/262 (Cl)

R_f value: 0.40 (silica gel, dichloromethane / MeOH 9:1).

10

Intermediate product 35:



15 Z35a) (2-chloro-4-nitro-benzyl)-diethyl-amine

0.80 g (3.883 mmol) 2-chloro-1-chloromethyl-4-nitro-benzene was added to a solution of 2.60 mL (25.000 mmol) diethylamine in 50 mL THF and the mixture was refluxed for 8 h. The reaction mixture was evaporated down i. vac. and the residue was taken up in EtOAc. The org. phase was washed with water, dried over sodium sulphate and evaporated down i. vac. .

Yield: 0.750 g (80% of theory)

C₁₁H₁₅CIN₂O₂ (M= 242.707)

Calc.: molpeak (M+H)⁺: 243/245

Found: molpeak (M+H)⁺: 243/245 (Cl)

25 R_f value: 0.50 (Alox, petroleum ether).

Z35b) 3-chloro-4-diethylaminomethyl-phenylamine

A suspension of 0.700 g (2.884 mmol) (2-chloro-4-nitro-benzyl)-diethyl-amine

(Z35a) and 0.400 g Raney nickel in 20 mL THF was hydrogenated for 7.5 h at RT

and 25 psi. The catalyst was filtered off and the filtrate was evaporated down i. vac. . The crude product was purified by column chromatography (Alox, neutral, act. II-III, petroleum ether / EtOAc 4:1).

Yield: 0.510 g (83% of theory)

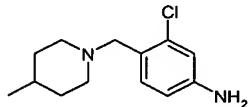
5 C₁₁H₁₇CIN₂ (M= 212.725)

Calc.: molpeak (M+H)⁺: 213/215

Found: molpeak (M+H)⁺: 213/215 (Cl)

R_f value: 0.58 (Alox, petroleum ether / EtOAc 3:1).

10 Intermediate product 36:



Z36a) 1-(2-chloro-4-nitro-benzyl)-4-methyl-piperidine

15 1.00 g (4.854 mmol) 2-chloro-1-chloromethyl-4-nitro-benzene was slowly added at RT to 2.00 mL (16.223 mmol) 4-methylpiperidine and the mixture was stirred for a further 15 min. . EtOAc was added, the org. phase was washed with water, dried over sodium sulphate and evaporated down i. vac. .

C₁₃H₁₇CIN₂O₂ (M= 268.746)

20 Calc.: molpeak (M+H)⁺: 269/271

Found: molpeak (M+H)⁺: 269/271 (Cl)

R_f value: 0.40 (Alox, petroleum ether).

Z36b) 3-chloro-4-(4-methyl-piperidin-1-ylmethyl)-phenylamine

25 Prepared analogously to Intermediate product Z35b starting from 1-(2-chloro-4-nitro-benzyl)-4-methyl-piperidine (Z36a). The crude product was purified by column chromatography (Alox, neutral, act. II-III, gradient petroleum ether / EtOAc 6:1 → 3:1).

Yield: 0.930 g (80% of theory)

$C_{13}H_{19}ClN_2$ ($M= 238.763$)

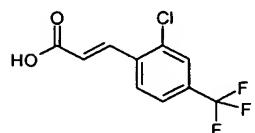
Calc.: molpeak ($M+H$) $^+$: 239/241

Found: molpeak ($M+H$) $^+$: 239/241 (Cl)

R_f value: 0.58 (Alox, petroleum ether / EtOAc 3:1).

5

Intermediate product 37:



10 Z37a) ethyl (E)-3-(2-chloro-4-trifluoromethyl-phenyl)-acrylate
0.157 g (0.686 mmol) palladium(II)acetate, 0.800 g (2.550 mmol) tri-o-tolylphosphine and 23.94 mL (171.73 mmol) triethylamine was added to 21.48 g (68.69 mmol) 2-chloro-1-iodo-4-trifluoromethyl-benzene and 10.45 mL (96.17 mmol) ethyl acrylate in 100 mL acetonitrile and the mixture was refluxed for 6 h.

15 The reaction mixture was evaporated down i. vac. and the residue triturated with EtOAc. The precipitate was filtered off and dried in a HV. The crude product was used in the next reaction step without any further purification.
Yield: 19.1 g (quant. yield)
 $C_{12}H_{10}ClF_3O_2$ ($M= 278.661$)

20 R_f value: 0.65 (silica gel, petroleum ether / EtOAc 6:1).

Z37b) (E)-3-(2-chloro-4-trifluoromethyl-phenyl)-acrylic acid

A solution of 5.80 g (145.00 mmol) NaOH in 30 mL water was slowly added to a solution of 19.1 g (68.61 mmol) (E)-3-(2-chloro-4-trifluoromethyl-phenyl)-acrylate ethyl (Z37a) in 100 mL EtOH and the mixture was stirred for 1 h at RT. EtOH was concentrated by evaporation i. vac., the aqueous phase was washed with EtOAc and acidified to pH 1 with semiconc. aqueous HCl. The precipitate was filtered off, washed with water and dried in a HV.

Yield: 15.80 g (92% of theory)

$C_{10}H_6ClF_3O_2$ ($M = 250.606$)

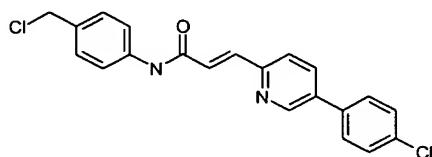
Calc.: molpeak ($M+H$) $^+$: 249/250

Found: molpeak ($M+H$) $^+$: 249/250 (Cl)

R_f value: 0.50 (silica gel, petroleum ether / EtOAc 3:1).

5

Intermediate product 38:



10 Z38a) (E)-3-[5-(4-chloro-phenyl)-pyridin-2-yl]-N-(4-hydroxymethyl-phenyl)-acrylamide

90 μ L (0.720 mmol) isobutyl chloroformate was added dropwise at -6 °C to a solution of 0.180 g (0.690 mmol) (E)-3-[5-(4-chloro-phenyl)-pyridin-2-yl]-acrylic acid (Z34b) and 80 μ L (0.720 mmol) N-methylmorpholine in 5 mL abs. DMF and

15 the mixture was stirred for 5 min.. 90 mg (0.720 mmol) 4-amino-benzylalcohol was added and the mixture was stirred for 2 h. The reaction mixture was poured onto water and the precipitate was filtered off. The precipitate was suspended in toluene, concentrated by evaporation i. vac., then stirred with ether and dried i. vac. at 80 °C .

20 Yield: 0.210 g (83% of theory)

$C_{21}H_{17}ClN_2O_2$ ($M = 364.835$)

Calc.: molpeak ($M+H$) $^+$: 365/367

Found: molpeak ($M+H$) $^+$: 365/367 (Cl)

R_f value: 0.30 (silica gel, dichloromethane / MeOH / HOAC 90:10:0.1).

25

Z38b) (E)-N-(4-chloromethyl-phenyl)-3-[5-(4-chloro-phenyl)-pyridin-2-yl]-acrylamide

50 μ L (0.680 mmol) thionyl chloride was added to a suspension of 0.190 g (0.520 mmol) (E)-3-[5-(4-chloro-phenyl)-pyridin-2-yl]-N-(4-hydroxymethyl-phenyl)-acrylamide (Z38a) in 20 mL dichloromethane and the mixture was stirred for 2 h at RT. Another 50 μ L thionyl chloride were added and the mixture was again stirred for 3 h. The solvent was concentrated by evaporation i. vac., the residue taken up twice in toluene and concentrated by evaporation i. vac.. The crude product was obtained as the HCl salt and used in the next reaction step without any further purification.

Yield: 0.132 g (60% of theory)

10 C₂₁H₁₆Cl₂N₂O * HCl (M= 419.741)

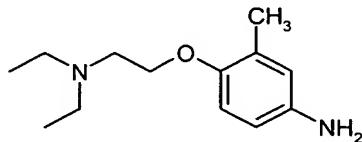
Calc.: molpeak (M+H)⁺: 383/385/387

Found: molpeak (M+H)⁺: 383/385/387 (Cl₂)

R_f value: 0.90 (silica gel, dichloromethane / MeOH / conc. aqueous ammonia 90:10:0.1).

15

Intermediate product 39:



Z39a) diethyl-[2-(2-methyl-4-nitro-phenoxy)-ethyl]-amine

At 0 °C 0.92 g (19.2 mmol) sodium hydride (50% in oil) was added to a solution of 20 2.70 g (17.4 mmol) 2-fluoro-5-nitro-toluene and 2.54 mL (19.2 mmol) 2-diethylaminoethanol in 50 mL DMF under an argon atmosphere and the mixture was stirred for 2 hours at 0 °C and for 1 hour at ambient temperature. The solvent was removed, the residue was taken up in ethyl acetate and extracted with water. The organic phase was dried over sodium sulphate and evaporated down i. vac. .
25 Then it was purified by silica gel column chromatography with dichloromethane/methanol 9:1 as eluant.
Yield: 3.1 g (71% of theory)

$C_{13}H_{20}N_2O_3$ ($M= 252.31$)

Calc.: molpeak ($M+H$) $^+$: 253

Found: molpeak ($M+H$) $^+$: 253

R_f value: 0.60 (silica gel, dichloromethane / MeOH 9:1)

5

Z39b) 4-(2-diethylamino-ethoxy)-3-methyl-phenylamine

3.10 g (12.3 mmol) diethyl-[2-(2-methyl-4-nitro-phenoxy)-ethyl]-amine were dissolved in 250 mL ethyl acetate, 0.55 g Raney nickel was added and the mixture was hydrogenated for 36 hours at 50 psi and ambient temperature. The catalyst

10 was filtered off and the filtrate evaporated down i. vac. .

Yield: 2.70 g (99% of theory)

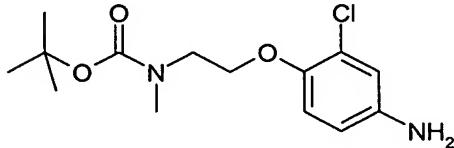
$C_{13}H_{22}N_2O$ ($M= 222.33$)

Calc.: molpeak ($M+H$) $^+$: 223

Found: molpeak ($M+H$) $^+$: 223

15 R_f value: 0.35 (silica gel, dichloromethane/methanol 9:1)

Intermediate product 40:



Z40a) N-tert.butoxycarbonyl-N-methyl-[2-(2-chloro-4-nitro-phenoxy)-ethyl]-amine

20 The product was obtained analogously to Intermediate product 29a starting from 2.00 g (11.4 mmol) 3-chloro-4-fluoro-nitrobenzene, 2.10 g (12.0 mmol) N-tert.butoxycarbonyl-N-methyl-aminoethanol and 820 mg (17.1 mmol) sodium hydride (50% in oil).

Yield: 3.77 g (100 % of theory)

25 $C_{14}H_{19}ClN_2O_5$ ($M= 330.77$)

R_f value: 0.35 (silica gel, petroleum ether/ethyl acetate 4:1)

Z40b) 4-(N-tert.butoxycarbonyl-2-methylamino-ethoxy)-3-chloro-phenylamine

The product was obtained analogously to Intermediate product 29b starting from 4.19 g (12.7 mmol) N-tert.butoxycarbonyl-N-methyl-[2-(2-chloro-4-nitro-phenoxy)-ethyl]-amine by hydrogenation with 500 mg Raney nickel at 3 bar.

5 Yield: 3.68 g (94 % of theory)

$C_{14}H_{21}ClN_2O_3$ ($M= 300.78$)

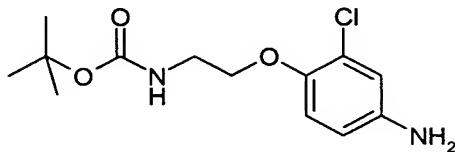
Calc.: molpeak $(M+H)^+$: 301/303

Found: molpeak $(M+H)^+$: 301/303

R_f value: 0.60 (silica gel, dichloromethane/methanol 19:1)

10

Intermediate product 41:



Z41a) N-tert.butoxycarbonyl-[2-(2-chloro-4-nitro-phenoxy)-ethyl]-amine

The product was obtained analogously to Intermediate product 29a starting from
 5 2.00 g (11.4 mmol) 3-chloro-4-fluoro-nitrobenzene, 1.85 mL (12.0 mmol) N-tert.butoxycarbonyl-aminoethanol and 820 mg (17.1 mmol) sodium hydride (50% in oil).

Yield: 2.25 g (62 % of theory)

$\text{C}_{13}\text{H}_{17}\text{ClN}_2\text{O}_5$ ($M= 316.74$)

10 Calc.: molpeak ($\text{M}-\text{H}^-$): 315/317

Found: molpeak ($\text{M}-\text{H}^-$): 315/317

R_f value: 0.45 (silica gel, petroleum ether/ethyl acetate 4:1)

Z41b) 4-(N-tert.butoxycarbonyl-2-amino-ethoxy)-3-chloro-phenylamine

15 The product was obtained analogously to Intermediate product 29b starting from 2.25 g (7.10 mmol) N-tert.butoxycarbonyl-[2-(2-chloro-4-nitro-phenoxy)-ethyl]-amine by hydrogenation with 500 mg Raney nickel at 3 bar.

Yield: 1.95 g (81 % of theory)

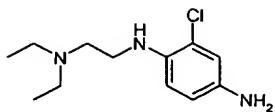
$\text{C}_{13}\text{H}_{19}\text{ClN}_2\text{O}_3$ ($M= 286.76$)

20 Calc.: molpeak ($\text{M}+\text{H}^+$): 287/289

Found: molpeak ($\text{M}+\text{H}^+$): 287/289

R_f value: 0.55 (silica gel, dichloromethane/methanol 19:1)

25 Intermediate product 42:



Z42a) *N*-(2-chloro-4-nitro-phenyl)-*N,N*-diethyl-ethane-1,2-diamine

9.440 g (34.120 mmol) potassium carbonate was added to a solution of 4.96 mL

5 (34.160 mmol) *N,N'*-diethyl-ethane-1,2-diamine in 64 mL DMF and the mixture
was stirred for for 15 min. at RT. 6.120 g (68.240 mmol) 2-chloro-1-fluoro-4-nitro-
benzene was added and the resulting mixture was stirred for 16 h at RT. The
reaction mixture was poured onto ice water, the precipitate was filtered off and
purified by column chromatography (Alox, neutral, act. II-III, dichloromethane /

10 MeOH 49:1).

Yield: 9.20 g (99 % of theory)

C₁₂H₁₈CIN₃O₂ (M= 271.749)

Calc.: molpeak (M+H)⁺: 272/274

Found: molpeak (M+H)⁺: 272/274

15 R_f value: 0.72 (Alox, dichloromethane/methanol 49:1)

Z42b) 2-chloro-*N*'-(2-diethylamino-ethyl)-benzene-1,4-diamine

A suspension of 8.850 g (32.570 mmol) *N*-(2-chloro-4-nitro-phenyl)-*N,N*-diethyl-
ethane-1,2-diamine and 4.00 g Raney nickel in 200 mL THF was hydrogenated for

20 7 h at 20 psi hydrogen pressure. The catalyst was filtered off, the filtrate
evaporated down i. vac. and the residue purified by column chromatography
(Alox, neutral, act. II-III, gradient dichloromethane / MeOH 100:0 → 24:1).

Yield: 6.150 g (78 % of theory)

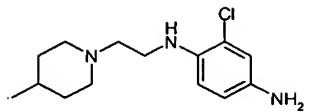
C₁₂H₂₀CIN₃ (M= 241.766)

25 Calc.: molpeak (M+H)⁺: 242/244

Found: molpeak (M+H)⁺: 242/244

R_f value: 0.62 (Alox, dichloromethane/methanol 49:1)

Intermediate product 43:



Z43a) tert-butyl [2-(4-methyl-piperidin-1-yl)-ethyl]-carbaminate

5 A solution of 10.00 g (43.280 mmol) tert-butyl (2-bromo-ethyl)-carbaminate and 11.60 mL (96.000 mmol) 4-methyl-piperidine in 100 mL dichloromethane was stirred for 16 h at RT. The crude product was filtered through Alox (neutral, act. II-III, dichloromethane / MeOH 49:1) and the filtrate was evaporated down i. vac. .
Yield: 6.150 g (78 % of theory)

10 $\text{C}_{13}\text{H}_{26}\text{N}_2\text{O}_2$ ($M= 242.364$)

Calc.: molpeak ($\text{M}+\text{H}$) $^+$: 243

Found: molpeak ($\text{M}+\text{H}$) $^+$: 243

R_f value: 0.65 (Alox, dichloromethane/methanol 19:1)

15 Z43b) 2-(4-methyl-piperidin-1-yl)-ethylamine-bis-trifluoroacetate

11.56 mL (150 mmol) TFA was added at RT to a solution of 8.500 g (35.070 mmol) tert-butyl [2-(4-methyl-piperidin-1-yl)-ethyl]-carbaminate in 100 mL dichloromethane and the mixture was stirred for 16 h at RT. The reaction mixture was evaporated down i. vac. and the residue stirred with ether. The precipitate
20 was filtered off, washed with ether and dried in a HV. The product was obtained as the bis-trifluoroacetate salt.

Yield: 12.10 g (93 % of theory)

$\text{C}_8\text{H}_{18}\text{N}_2 * 2 \text{C}_2\text{HF}_3\text{O}_2$ ($M= 370.295$)

Calc.: molpeak ($\text{M}+\text{H}$) $^+$: 143

25 Found: molpeak ($\text{M}+\text{H}$) $^+$: 143

Z43c) (2-chloro-4-nitro-phenyl)-[2-(4-methyl-piperidin-1-yl)-ethyl]-amine

Prepared analogously to Intermediate product Z42a starting from 12.02 g (32.450 mmol) 2-(4-methyl-piperidin-1-yl)-ethylamine-bis-trifluoroacetate, 5.810 g (32.450

mmol) 2-chloro-1-fluoro-4-nitro-benzene and 17.94 g (129.64 mmol) potassium carbonate.

Yield: 8.85 g (92% of theory)

$C_{14}H_{20}ClN_3O_2$ ($M= 297.787$)

5 Calc.: molpeak ($M+H$)⁺: 298/300

Found: molpeak ($M+H$)⁺: 298/300

Z43d) 2-chloro-*N'*-[2-(4-methyl-piperidin-1-yl)-ethyl]-benzene-1,4-diamine

Prepared analogously to Intermediate product Z42b starting from 8.715 g (29.270

10 mmol) (2-chloro-4-nitro-phenyl)-[2-(4-methyl-piperidin-1-yl)-ethyl]-amine.

Yield: 7.00 g (89 % of theory)

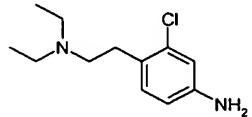
$C_{14}H_{22}ClN_3$ ($M= 267.805$)

Calc.: molpeak ($M+H$)⁺: 268/280

Found: molpeak ($M+H$)⁺: 268/280 (Cl)

15 R_f value: 0.60 (Alox, dichloromethane/methanol 49:1)

Intermediate product 44:



20

Z44a) (2-chloro-4-nitro-phenyl)-acetyl-chloride

A suspension of 8.100 g (37.571 mmol) (2-chloro-4-nitro-phenyl)-acetic acid in 40 mL thionyl chloride was refluxed for 2 h, cooled to RT and evaporated down i. vac.

. The crude product was used in the next reaction step without any further

25 purification.

Yield: 8.80 g (quant. yield)

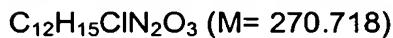
$C_8H_5Cl_2NO_3$ ($M= 234.040$)

Z44b) 2-(2-chloro-4-nitro-phenyl)-*N,N*-diethyl-acetamide

At 0 °C a solution of 3.20 g (13.673 mmol) (2-chloro-4-nitro-phenyl)-acetyl-chloride in 50 mL EtOAc was slowly added dropwise to a solution of 5.67 mL (54.000 mmol) diethylamine in 50 mL EtOAc, then the cooling bath was removed and the mixture was stirred for 2 h at RT . The reaction mixture was diluted with EtOAc ,

5 the org. phase was washed with water and saturated aqueous NaCl solution, dried over sodium sulphate and evaporated down i. vac. .

Yield: 3.70 g (quant. yield)



Calc.: molpeak $(\text{M}+\text{H})^+$: 271/273

10 Found: molpeak $(\text{M}+\text{H})^+$: 271/273 (Cl)

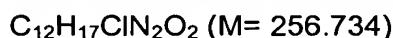
R_f value: 0.45 (silica gel, petroleum ether / EtOAc 1:1)

Z44c) [2-(2-chloro-4-nitro-phenyl)-ethyl]-diethyl-amine

65 mL (65.000 mmol) borane (1 M in THF) was added at RT to a solution of 3.702

15 g (13.673 mmol) 2-(2-chloro-4-nitro-phenyl)-*N,N*-diethyl-acetamide in 130 mL THF and the mixture was stirred for 4 h . The reaction mixture was evaporated down i. vac. , the residue was combined with 15 mL MeOH and 15 mL semiconc. aqueous HCl and heated to 100 °C for 15 min.. Water was added, the mixture was made basic with aqueous sodium carbonate solution and the aqueous phase was extracted with EtOAc . The combined org. phases were washed with water and saturated aqueous NaCl solution, dried over sodium sulphate and evaporated down i. vac. . The crude product was purified by column chromatography (Alox, neutral, act. II-III, gradient petroleum ether / EtOAc 8:1 → 4:1).

20 Yield: 2.10 g (60% of theory)



R_f value: 0.63 (Alox, petroleum ether / EtOAc 3:1)

Z44d) 3-chloro-4-(2-diethylamino-ethyl)-phenylamine

A suspension of 2.00 g (7.790 mmol) [2-(2-chloro-4-nitro-phenyl)-ethyl]-diethyl-

30 amine and 0.80 g Raney nickel in THF was hydrogenated for 2.5 h at RT and 25

psi hydrogen pressure. The catalyst was filtered off and the filtrate evaporated down i. vac. .

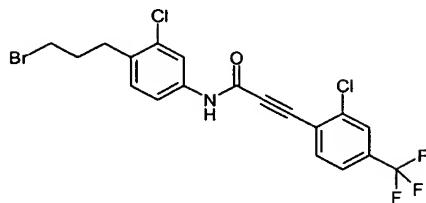
Yield: 3.70 g (quant. yield)

C₁₂H₁₉CIN₂ (M= 226.752)

5 Calc.: molpeak (M+H)⁺: 227/229

Found: molpeak (M+H)⁺: 227/229 (Cl)

Intermediate product 45:



5 Z45a) 3-(2-chloro-4-nitro-phenyl)-prop-2-yn-1-ol

1.059 mL (18.000 mmol) propargylalcohol was added under argon to 5.013 g (21.200 mmol) 4-bromo-3-chloronitrobenzene, 8.72 mL (63.000 mmol) triethylamine, 1.265 g (1.800 mmol) bis(triphenylphosphine)-palladium(II)dichloride and 0.343 g (1.800 mmol) copper(I)iodide in 50 mL acetonitrile and the mixture
 10 was refluxed for 4 h. The reaction mixture was filtered through Celite and the filtrate was evaporated down i. vac. . The residue was dissolved in EtOAc, the org. phase was washed with water, dried over sodium sulphate and evaporated down i. vac. . The crude product was purified by column chromatography (silica gel, petroleum ether / EtOAc 3:1) and by trituration with petroleum ether.

15 Yield: 2.550 g (67% of theory)

$C_9H_6ClNO_3$ ($M= 211.606$)

Calc.: molpeak ($M+H$)⁺: 211/213

Found: molpeak ($M+H$)⁺: 211/213 (Cl)

R_f value: 0.38 (silica gel, dichloromethane / MeOH 50:1)

20

Z45b) 3-(2-chloro-4-nitro-phenyl)-propan-1-ol

A suspension of 1.25 g (6.808 mmol) 3-(2-chloro-4-nitro-phenyl)-prop-2-yn-1-ol and 1.00 g Raney nickel in 50 mL THF was hydrogenated for 12 h at RT and 25 psi hydrogen pressure. The catalyst was filtered off and the filtrate was evaporated
 25 down i. vac. .

Yield: 1.26 g (quant. yield)

$C_9H_{12}ClNO$ ($M= 185.655$)

Calc.: molpeak (M+H)⁺: 186/188

Found: molpeak (M+H)⁺: 186/188 (Cl)

R_f value: 0.33 (silica gel, dichloromethane / MeOH 19:1)

5 Z45c) (E)-N-[3-chloro-4-(3-hydroxy-propyl)-phenyl]-3-(2-chloro-4-trifluoromethyl-phenyl)-acrylamide

Prepared analogously to Intermediate product Z32a starting from (E)-3-(2-chloro-4-trifluoromethyl-phenyl)-acrylic acid (Z37b) and 3-(2-chloro-4-nitro-phenyl)-propan-1-ol. The crude product was purified by column chromatography (silica gel,

10 petroleum ether / EtOAc 1:1).

Yield: 1.800 g (63% of theory)

C₁₉H₁₆Cl₂F₃NO₂ (M= 418.246)

Calc.: molpeak (M+H)⁺: 418/420/422

Found: molpeak (M+H)⁺: 418/420/422 (Cl₂)

15

Z45d) (E)-N-[4-(3-bromo-propyl)-3-chloro-phenyl]-3-(2-chloro-4-trifluoromethyl-phenyl)-acrylamide

0.577 g (2.200 mmol) triphenylphosphine was added batchwise to a suspension of 0.836 g (2.000 mmol) (E)-N-[3-chloro-4-(3-hydroxy-propyl)-phenyl]-3-(2-chloro-4-

20 trifluoromethyl-phenyl)-acrylamide and 0.730 g (2.200 mmol) tetrabromomethane in 10 mL dichloromethane and the mixture was stirred for 48 h at RT. The reaction mixture was purified by column chromatography (silica gel, dichloromethane) and the residue was triturated with petroleum ether.

Yield: 0.620 g (64% of theory)

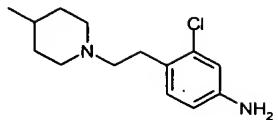
25 C₁₉H₁₅BrCl₂F₃NO (M= 481.143)

Calc.: molpeak (M+H)⁺: 480/482/484/486

Found: molpeak (M+H)⁺: 480/482/484/486 (BrCl₂)

R_f value: 0.81 (silica gel, dichloromethane)

30 Intermediate product 46:



Z46a) 2-(2-chloro-4-nitro-phenyl)-1-(4-methyl-piperidin-1-yl)-ethanone

Prepared analogously to Intermediate product Z44b starting from (2-chloro-4-nitro-phenyl)-acetyl-chloride (Z44a) and 4-methylpiperidine.

Yield: 1.050 g (77% of theory)

C₁₄H₁₇CIN₂O₃ (M= 296.756)

R_f value: 0.51 (silica gel, petroleum ether / EtOAc 1:1)

10 Z46b) 1-[2-(2-chloro-4-nitro-phenyl)-ethyl]-4-methyl-piperidine

Prepared analogously to Intermediate product Z44c starting from (2-chloro-4-nitro-phenyl)-1-(4-methyl-piperidin-1-yl)-ethanone. The crude product was purified by column chromatography (Alox, neutral, act. II-III, gradient petroleum ether / EtOAc 8:1 → 6:1).

15 Yield: 0.820 g (57% of theory)

C₁₄H₁₉CIN₂O₂ (M= 282.773)

R_f value: 0.73 (silica gel, petroleum ether / EtOAc 2:1)

Z46c) 3-chloro-4-[2-(4-methyl-piperidin-1-yl)-ethyl]-phenylamine

20 Prepared analogously to Intermediate product Z44d starting from 1-[2-(2-chloro-4-nitro-phenyl)-ethyl]-4-methyl-piperidine.

Yield: 0.820 g (57% of theory)

C₁₄H₂₁CIN₂ (M= 252.790)

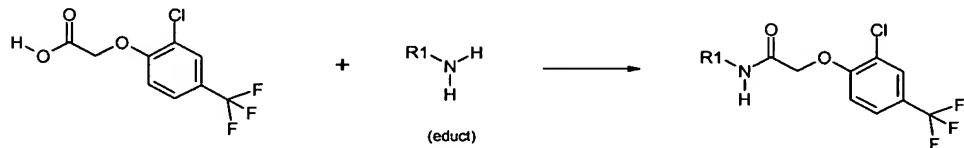
Calc.: molpeak (M+H)⁺: 253/255

25 Found: molpeak (M+H)⁺: 253/255 (Cl)

G General working method I (TBTU coupling):

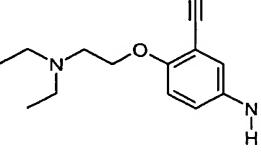
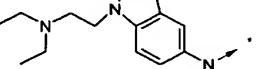
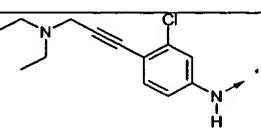
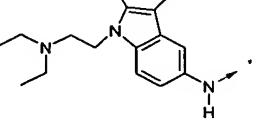
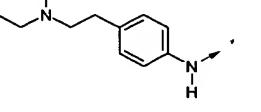
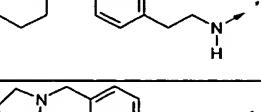
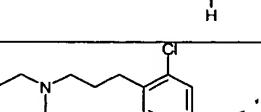
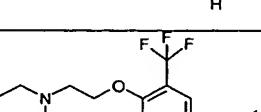
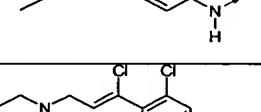
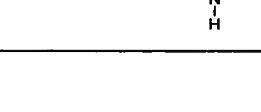
Triethylamine (1.5 eq.) or N-ethyldiisopropylamine (1.5eq.) and TBTU (1.0-1.5 eq.)
 5 are added successively to a solution of carboxylic acid (1.0 eq.) in THF or DMF.
 Depending on the carboxylic acid the mixture is stirred for 10 minutes - 12 hours
 between ambient temperature and 40°C before the amine (1.0 eq.) is added. The
 reaction is stirred for 30 minutes - 24 hours between ambient temperature and
 10 40°C, before semisaturated NaHCO₃ solution is added. After extraction of the
 aqueous phase with EtOAc the organic phase is dried over magnesium sulphate.
 The solvent is removed using the rotary evaporator; further purification is carried
 out by column chromatography or crystallisation. The reaction may also be carried
 out in a Chemspeed automatic synthesiser.

15 The following compounds were prepared according to general working method I:



while in the Table that follows the products are defined by the partial formula R¹-
 20 NH- and the associated carboxylic acid educts are defined by reference to the
 corresponding Example number of the intermediate product.

Example	R ¹ NH-	Educt	Empirical formula	Mass spectrum	R _f value	Yield (%)
1		Z10	C ₂₂ H ₂₃ Cl ₂ F ₃ N ₂ O ₃	491/493 [M+H] ⁺	0.45 (A)	44

2		Z11b	C ₂₂ H ₂₃ ClF ₃ N ₃ O ₃	470/472 [M+H] ⁺	0.36 (A)	64
3		Z12b	C ₂₃ H ₂₇ ClF ₃ N ₃ O ₂	470/472 [M+H] ⁺	0.22 (A)	44
4		Z13b	C ₂₂ H ₂₁ Cl ₂ F ₃ N ₂ O ₂	473/475/477 [M+H] ⁺	0.42 (A)	21
5		Z14b	C ₂₅ H ₂₉ ClF ₃ N ₃ O ₂	496/498 [M+H] ⁺	0.30 (A)	48
6		Lit.	C ₂₁ H ₂₄ ClF ₃ N ₂ O ₂	429/431 [M+H] ⁺	0.33 (A)	36
7		Z24b	C ₂₃ H ₂₆ ClF ₃ N ₂ O ₂	455/457 [M+H] ⁺	0.46 (A)	50
8		Z23f	C ₂₂ H ₂₄ ClF ₃ N ₂ O ₂	441/443 [M+H] ⁺	0.37 (A)	46
9		Z15	C ₂₂ H ₂₅ Cl ₂ F ₃ N ₂ O ₂	477/479/481 [M+H] ⁺	0.22 (A)	31
10		Z16b	C ₂₂ H ₂₃ ClF ₆ N ₂ O ₃	513/515 [M+H] ⁺	0.27 (A)	39
11		Z17	C ₂₂ H ₂₂ Cl ₃ F ₃ N ₂ O ₂	509/11/13/15 [M+H] ⁺	0.48 (A)	1

12		Z18b	C ₂₃ H ₂₅ ClF ₃ N ₃ O ₂	468/470 [M+H] ⁺	0.63 (A)	1
13		Z19b	C ₂₁ H ₂₅ ClF ₃ N ₃ O ₂	444/446 [M+H] ⁺	0.35 (A)	35
14		Z20b	C ₂₂ H ₂₆ Cl ₂ F ₃ N ₃ O ₂	492/494/49 6 [M+H] ⁺	0.46 (A)	49
15		Z21b	C ₂₄ H ₂₉ ClF ₃ N ₃ O ₂	484/486 [M+H] ⁺	0.86 (B)	42

Lit.: known from the literature

5 Eluant: A) dichloromethane / MeOH / conc. aqueous ammonia = 90:10:1
 B) EtOAc / MeOH / conc. aqueous ammonia = 90:10:1

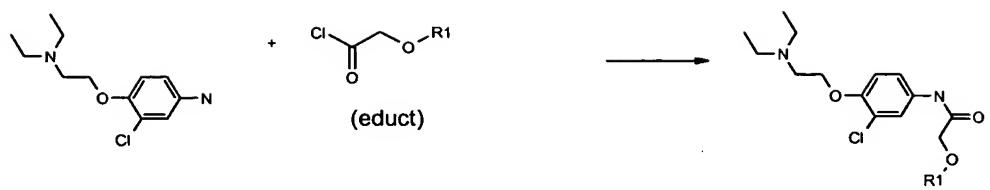
General working method II:

10

A solution of 1.0 eq. acid chloride in THF is slowly added dropwise to a solution of 1.0 eq. of 3-chloro-4-(2-diethylaminoethoxy)-phenylamine and 4.5-6.0 eq. of triethylamine in THF at 5°C. The reaction mixture is stirred for 3 hours at 25-30°C, filtered off and washed with THF. The filtrate is evaporated down i. vac. and the

15 residue purified by column chromatography. The intermediate product is dissolved in acetonitrile, acidified with ethereal HCl and precipitated with ether. Further purification is carried out by recrystallisation.

According to general working method II the following compounds were prepared:

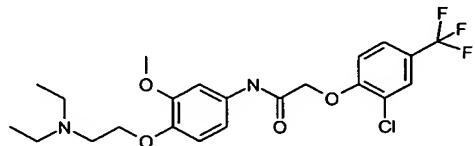


while in the Table that follows the products are defined by means of the group R¹.
The associated amino educts are commercially available and/or known from the literature.

5

Example	R ¹	Empirical formula	Melting point	Yield (%)
16		C ₂₀ H ₂₃ Cl ₃ N ₂ O ₃ x HCl	186-188°C	63
17		C ₂₀ H ₂₄ Cl ₂ N ₂ O ₃ x HCl	171-172°C	62
18		C ₂₀ H ₂₄ Cl ₂ N ₂ O ₃ x HCl	183-185°C	63

Example 19:



10 19) 2-(2-chloro-4-trifluoromethyl-phenoxy)-N-[4-(2-diethylaminoethoxy)-3-methoxy-phenyl]-acetamide
171 mg (0.82 mmol) of CDI was added to a solution of 185 mg (0.73 mmol) of (2-chloro-4-trifluoromethyl-phenoxy)-acetic acid (cf intermediate product Z2b) in 5 mL

tetrahydrofuran and the reaction mixture was stirred for 30 minutes at 50°C. Then 0.1 mL (0.73 mmol) of triethylamine and 200 mg (0.73 mmol) of 4-(2-diethylaminoethoxy)-3-methoxy-phenylamine (see intermediate product Z6b) were added and the solution was stirred for 16 hours at RT. The reaction solution was added to 5 water and stirred for 45 minutes at RT. After filtration the residue was dried in the circulating air dryer.

Yield: 170 mg (49 % of theory)

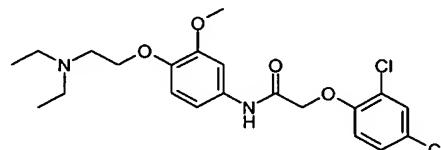
$C_{22}H_{26}ClF_3N_2O_4$ ($M= 474.912$)

Calc.: Molpeak($M+H$) $^+$: 475/477

10 Found: Molpeak ($M+H$) $^+$: 475/477 (Cl)

R_f value: 0.30 (silica gel, dichloromethane / MeOH / conc. aqueous ammonia 90:10:1).

Example 20:



15

20) 2-(2,4-dichlorophenoxy)-N-[4-(2-diethylaminoethoxy)-3-methoxyphenyl]acetamide

A solution of 70 mg (0.290 mmol) of (2,4-dichlorophenoxy)-acetylchloride in 0.5 mL dichloromethane was added to a solution of 66 mg (0.278 mmol) of 4-(2-

20 diethylaminoethoxy)-3-methoxy-phenylamine (intermediate product Z6b) and 96 μ L (0.56 mmol) of ethyl-diisopropylamine in 1.5 mL abs. dichloromethane and the mixture was stirred for 15 hours at RT. The reaction mixture was evaporated down i. vac. and the residue was purified by column chromatography (silica gel, dichloromethane / MeOH 9:1).

25 Yield: 77 mg (61 % of theory)

$C_{21}H_{26}Cl_2N_2O_4$ ($M= 441.358$)

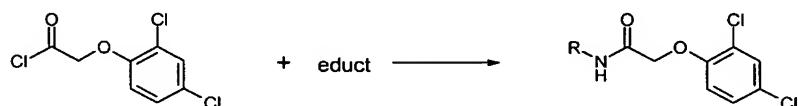
Calc.: Molpeak($M+H$) $^+$: 441/443/445

Found: Molpeak (M+H)⁺: 441/443/445

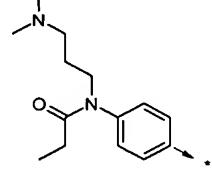
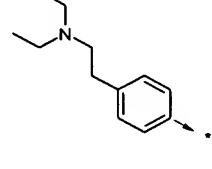
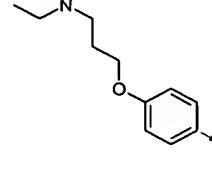
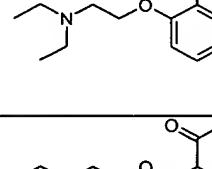
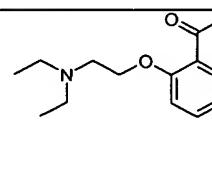
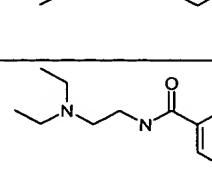
R_f value: 0.32 (silica gel, dichloromethane / MeOH 9:1)

The following compounds were prepared analogously to Example 20:

5



while in the Table that follows the products are defined by means of the group R
and the associated educts are defined by reference to the corresponding Example
10 number of the intermediate product or are given as known from the literature (Lit.).

Exa mpl e	R	Educt	Empirical formula	Mass spectrum	R _f valu e	Yield (%)
21		Lit.	C ₂₂ H ₂₇ Cl ₂ N ₃ O ₃	452/454/457 [M+H] ⁺	0.12 (A)	65 %
22		Lit.	C ₂₀ H ₂₄ Cl ₂ N ₂ O ₂	395/397/399 [M+H] ⁺	0.38 (A)	46 %
23		Lit.	C ₂₁ H ₂₆ Cl ₂ N ₂ O ₃	425/427/429 [M+H] ⁺	0.31 (A)	69 %
24		Z8b	C ₂₀ H ₂₃ Cl ₂ FN ₂ O ₃	429/431/433 [M+H] ⁺	0.34 (A)	66 %
25		Z7b	C ₂₂ H ₂₆ Cl ₂ N ₂ O ₅	469/471/473 [M+H] ⁺	0.30 (A)	40 %
26		Z5b	C ₂₀ H ₂₄ Cl ₂ N ₂ O ₃	411/413/415 [M+H] ⁺	0.33 (A)	89 %
27		Lit.	C ₂₁ H ₂₅ Cl ₂ N ₃ O ₃	438/440/442 [M+H] ⁺	0.28 (A)	52 %

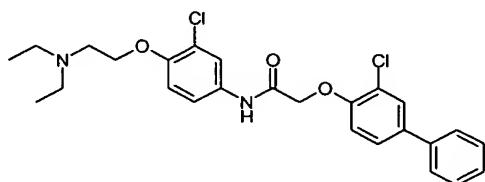
28		Z23c	C ₁₉ H ₂₃ Cl ₂ N ₃ O ₄ S	460/462 [M+H] ⁺	0.40 (A)	36 %
29		Z9c	C ₂₅ H ₃₉ Cl ₂ N ₃ O ₃	496/498/500 [M+H] ⁺	0.21 (A)	84 %
30		Lit.	C ₁₉ H ₂₂ Cl ₂ N ₂ O ₂	381/383 [M+H] ⁺	0.48 (A)	35 %
31		Lit.	C ₂₀ H ₂₃ Cl ₂ N ₃ O ₂	408/410/412 [M+H] ⁺	0.35 (A)	40 %

R_f value: A= (silica gel, dichloromethane / MeOH 9:1)

B= (silica gel, EtOAc)

5

Example 32:



32) 2-(3-chloro-biphenyl-4-yloxy)-N-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-acetamide

10 65 mg (0.47 mmol) of potassium carbonate was added to a solution of 70 mg (0.159 mmol) of 2-bromo-N-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-acetamide-hydrobromide (intermediate product Z1c) and 64 mg (0.314 mmol) of 3-chloro-biphenyl-4-ol in 1 mL of abs. DMF and the mixture was stirred for 1 hour at 40 °C and for 15 hours at RT. The reaction mixture was diluted with

dichloromethane, the org. phase was washed with sat. aqueous sodium bicarbonate solution and water and dried over magnesium sulphate. Column chromatography (silica gel, dichloromethane / MeOH 9:1) yielded the product. Yield: 51 mg (67 % of theory)

5 $C_{26}H_{28}Cl_2N_2O_3$ ($M= 487.431$)

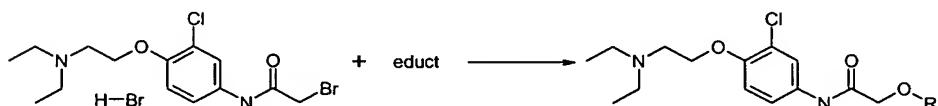
Calc.: Molpeak($M+H$)⁺: 487/489/491

Found: Molpeak ($M+H$)⁺: 487/489/491 (Cl_2)

R_f value: 0.43 (silica gel, dichloromethane / MeOH 9:1)

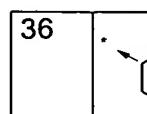
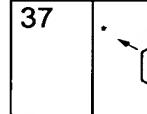
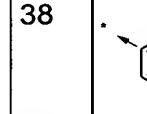
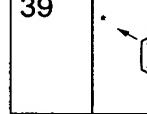
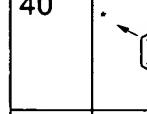
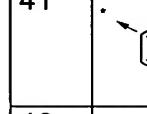
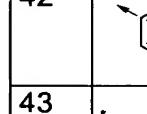
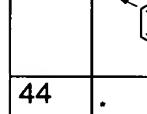
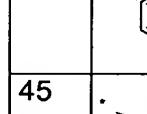
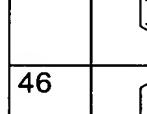
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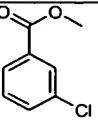
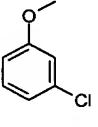
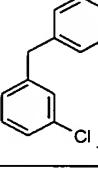
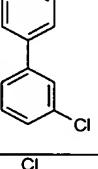
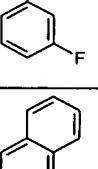
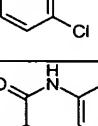
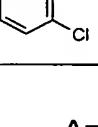
The following compounds were prepared analogously to Example 32:



15 while in the Table that follows the products are defined by means of the group R and the associated educts are commercially available.

Exa mpl e	R	Empirical formula	Mass spectrum	R_f value	Yield (%)
33		$C_{21}H_{23}Cl_2F_3N_2O_3$	479/481/483 [$M+H$] ⁺	0.34 (A)	67 %
34		$C_{24}H_{32}Cl_2N_2O_3$	467/469/471 [$M+H$] ⁺	0.31 (A)	63 %
35		$C_{22}H_{26}Cl_2N_2O_5$	469/471/473 [$M+H$] ⁺	0.30 (A)	80 %

36		C ₂₀ H ₂₃ Br ₂ CIN ₂ O ₃	533/535/537 [M+H] ⁺	0.31 (A)	82 %
37		C ₂₀ H ₂₃ BrCl ₂ N ₂ O ₃	489/491/495/4 95 [M+H] ⁺	0.25 (A)	74 %
38		C ₂₄ H ₂₆ BrCIN ₂ O ₃	505/507/509 [M+H] ⁺	0.36 (A)	80 %
39		C ₂₁ H ₂₆ Cl ₂ N ₂ O ₄	441/443/445 [M+H] ⁺	0.38 (A)	60 %
40		C ₂₁ H ₂₆ Cl ₂ N ₂ O ₃	425/427/429 [M+H] ⁺	0.31 (A)	85 %
41		C ₂₀ H ₂₃ BrCl ₂ N ₂ O ₃	489/491/493/4 95 [M+H] ⁺	0.32 (A)	57 %
42		C ₂₄ H ₂₇ CIN ₂ O ₃	427/429 [M+H] ⁺	0.31 (A)	78 %
43		C ₂₂ H ₂₉ CIN ₂ O ₃	405/407 [M+H] ⁺	0.30 (A)	73 %
44		C ₂₀ H ₂₃ Cl ₂ FN ₂ O ₃	429/431/433 [M+H] ⁺	0.26 (A)	74 %
45		C ₂₁ H ₂₆ Cl ₂ N ₂ O ₃	425/427/429 [M+H] ⁺	0.19 (A)	54 %
46		C ₂₆ H ₃₄ Cl ₂ N ₂ O ₃	493/495/497 [M+H] ⁺	0.24 (A)	62 %

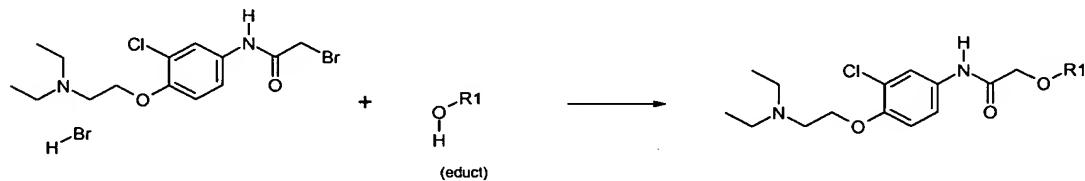
47		C ₂₂ H ₂₆ Cl ₂ N ₂ O ₅	469/471/473[M+H] ⁺	0.25 (A)	68 %
48		C ₂₁ H ₂₆ Cl ₂ N ₂ O ₄	441/443/445 [M+H] ⁺	0.31 (A)	80 %
49		C ₂₀ H ₂₃ Cl ₃ N ₂ O ₃	445/447/449/4 51[M+H] ⁺	0.26(A)	66 %
50		C ₂₇ H ₃₀ Cl ₂ N ₂ O ₃	501/503/505[M+H] ⁺	0.36 (A)	93 %
51		C ₂₆ H ₂₈ Cl ₂ N ₂ O ₃	487/489/491[M+H] ⁺	0.36 (A)	83 %
52		C ₂₀ H ₂₃ Cl ₂ FN ₂ O ₃	429/431/433[M+H] ⁺	0.36 (A)	64 %
53		C ₂₄ H ₂₇ CIN ₂ O ₃	427/429 [M+H] ⁺	0.32 (A)	84 %
54		C ₂₁ H ₂₅ Cl ₂ N ₃ O ₄	454/456/458[M+H] ⁺	0.08 (A)	72 %
55		C ₂₇ H ₂₉ Cl ₂ N ₃ O ₄	530/532/534[M+H] ⁺	0.23 (A)	48 %

R_f value: A= (silica gel, dichloromethane / MeOH 9:1)

5 General working method III (phenol alkylation I):

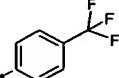
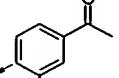
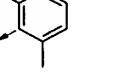
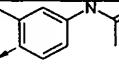
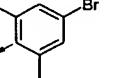
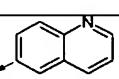
Phenol (2.0 eq.) and potassium carbonate (3.0-5.0 eq.) are added successively to a solution of the alkyl bromide (see intermediate product Z1c) (1.0 eq.) in DMF. The mixture is stirred for 48-72 hours at RT under a nitrogen atmosphere, before being added to water. After extraction of the aqueous phase with EtOAc the organic phase is dried over magnesium sulphate. The solvent is removed using the rotary evaporator; further purification is carried out by column chromatography or crystallisation.

10 According to general working method III the following compounds were prepared:



15 while in the Table that follows the products are defined by means of the group R₁ and the associated educts are commercially available.

Example	R1	Empirical formula	Mass spectrum	R _f value	Yield (%)
56		C ₂₁ H ₂₆ ClIN ₂ O ₃	517/519 [M+H] ⁺	0.32 (A)	47
57		C ₂₄ H ₂₆ BrClN ₂ O ₃	505/507/509 [M+H] ⁺	0.42 (A)	20
58		C ₂₁ H ₂₇ BrClN ₂ O ₃	469/471/473 [M+H] ⁺	0.33 (A)	49

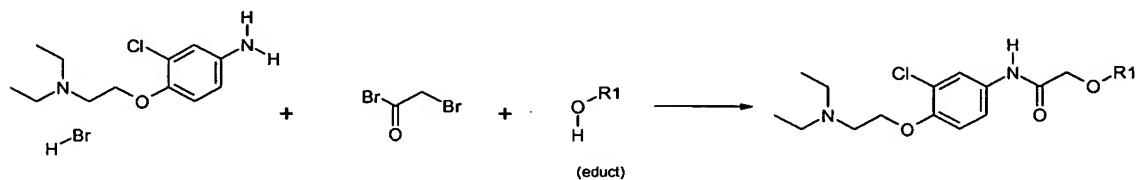
59		C ₁₁ H ₁₂ ClF ₂ N ₂ O ₃	445/447 [M+H] ⁺	0.32 (A)	56
60		C ₁₂ H ₁₄ ClN ₂ O ₄	433/435 [M+H] ⁺	0.37 (A)	23
61		C ₁₁ H ₁₂ Cl ₂ N ₂ O ₃	425/427/429 [M+H] ⁺	0.42 (A)	24
62		C ₁₂ H ₁₄ Cl ₂ N ₃ O ₄	468/470/472 [M+H] ⁺	0.26 (A)	21
63		C ₁₁ H ₁₂ BrClN ₂ O ₃	483/485/487 [M+H] ⁺	0.32 (A)	48
64		C ₁₂ H ₁₄ ClN ₃ O ₃	428/430 [M+H] ⁺	0.23 (A)	12

Eluant: A) dichloromethane / MeOH / ammonia = 90:10:1

5 General working method IV (phenolalkylation II):

Bromoacetyl bromide (1.0 eq.) in dioxane is added dropwise to a solution of the aniline (see intermediate product Z1b) (1.0 eq.) in DMF at -10°C. Then the mixture is heated to RT and phenol (1.0 eq.) in DMF and potassium-*tert*-butoxide (2.0 eq.) in *tert*-butanol are added successively. The mixture is heated to 80°C for 4 hours. DMF is eliminated in vacuo and the residue is dissolved in EtOAc. The ethyl acetate solution is washed 1x with 10 % K₂CO₃ solution, then 2x with water. The EtOAc is eliminated in vacuo. Further purification is carried out by column chromatography.

According to general working method IV the following compounds were prepared:



5

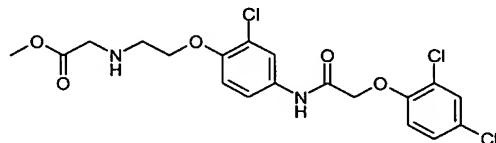
while in the Table that follows the products are defined by means of the group R1 and the associated educts are commercially available.

Example	R1	Empirical formula	Mass spectrum	R_f value	Yield (%)
65		C ₂₁ H ₂₃ ClF ₃ N ₃ O ₅	490/492 [M+H] ⁺	0.24 (A)	6
66		C ₂₀ H ₂₃ Cl ₂ N ₃ O ₅	456/458/460 [M+H] ⁺	0.28 (A)	7
67		C ₂₄ H ₂₅ Br ₂ ClN ₂ O ₅	583/85/87/89 [M+H] ⁺	0.50 (A)	7
68		C ₂₅ H ₂₉ ClN ₂ O ₄	455/457 [M+H] ⁺	0.24 (A)	13
69		C ₂₀ H ₂₂ Cl ₄ N ₂ O ₃	479/81/83/85/ 87 [M+H] ⁺	0.28 (A)	10
70		C ₂₀ H ₂₂ BrCl ₃ N ₂ O ₃	521/23/25/27 [M+H] ⁺	0.28 (A)	10
71		C ₂₀ H ₂₂ Cl ₄ N ₂ O ₃	477/79/81/83 [M+H] ⁺	0.23 (A)	8

72		C ₂₂ H ₂₇ ClN ₂ O ₄	419/421 [M+H] ⁺	0.25 (A)	5
73		C ₂₂ H ₂₇ Cl ₃ N ₂ O ₃	473/75/77/79 [M+H] ⁺	0.31 (A)	8
74		C ₂₁ H ₂₅ BrCl ₂ N ₂ O ₃	503/05/07/09 [M+H] ⁺	0.28 (A)	8

Eluant: A) dichloromethane / MeOH / ammonia = 90:10:1

Example 75:



5

75) methyl (2-{2-chloro-4-[2-(2,4-dichlorophenoxy)-acetylamo]phenoxy}-ethylamino)-acetate

75 μ L (0.54 mmol) of triethylamine and 70 mg (0.18 mmol) of N-[3-chloro-4-(2-oxoethoxy)-phenyl]-2-(2,4-dichlorophenoxy)-acetamide was added to a suspension of 10 45 mg (0.36 mmol) of methyl amino-acetate hydrochloride in 2 mL dichloromethane / THF (1:1). 114 mg (0.54 mmol) of sodium triacetoxyborohydride was added and the mixture was stirred for 3 hours at RT. 100 mL of 2 N aqueous sodium carbonate solution was added and the aqueous phase was exhaustively extracted with chloroform. The combined org. extracts were dried over magnesium 15 sulphate, evaporated down i. vac. and purified by column chromatography (silica gel, EtOAc / MeOH 9:1).

Yield: 71 mg (78 % of theory)

C₁₉H₁₉Cl₃N₂O₅ (M= 461.733)

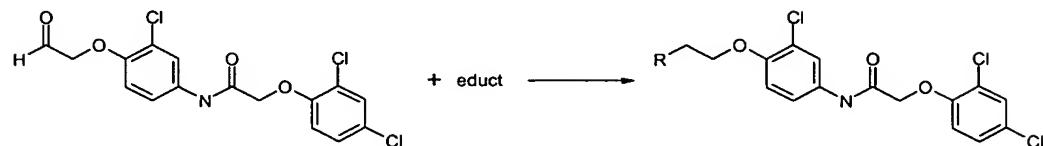
Calc.: Molpeak(M+H)⁺: 461/463/465/467

20 Found: Molpeak (M+H)⁺: 461/463/465/467 (Cl₃)

R_f value: 0.32 (silica gel, EtOAc)

The following compounds were prepared analogously to Example 75:

5



while in the Table that follows the products are defined by means of the group R and the associated educts are commercially available.

10

Exa mpl e	R	Empirical formula	Mass spectrum	R_f value	Yield (%)
76		$C_{21}H_{23}Cl_3N_2O_3$	457/459/461/463 [M+H] ⁺	0.30 (A)	66 %
77		$C_{20}H_{21}Cl_3N_2O_3$	443/445/447/449 [M+H] ⁺	0.28 (A)	70 %
78		$C_{20}H_{21}Cl_3N_2O_4$	459/461/463/465 [M+H] ⁺	0.18 (B)	72 %
79		$C_{28}H_{29}Cl_3N_2O_3$	547/549/551/553 [M+H] ⁺	0.19 (B)	52 %
80		$C_{21}H_{24}Cl_3N_3O_3$	472/474/476/478 [M+H] ⁺	0.31 (A)	66 %
81		$C_{20}H_{24}Cl_3N_3O_3$	460/462/464/466 [M+H] ⁺	0.19 (A)	42 %

82		C ₂₅ H ₂₃ Cl ₃ N ₂ O ₃	505/507/509/511 [M+H] ⁺	0.61 (B)	78 %
83		C ₂₂ H ₂₅ Cl ₃ N ₂ O ₃	471/473/475/477 [M+H] ⁺	0.41 (B)	64 %
84		C ₂₃ H ₂₁ Cl ₃ N ₂ O ₃	479/481/483/485 [M+H] ⁺	0.16 (B)	69 %
85		C ₂₈ H ₃₀ Cl ₃ N ₂ O ₃	583/585/587/589 [M+H] ⁺	0.51 (B)	56 %
86		C ₂₇ H ₂₈ Cl ₃ N ₃ O ₃	548/550/552/554 [M+H] ⁺	0.10 (B)	82 %
87		C ₂₂ H ₁₉ Cl ₃ N ₂ O ₃	465/467/469/471 [M+H] ⁺	0.51 (C)	58 %

R_f value: A= (silica gel, dichloromethane / MeOH 9:1)

B= (silica gel, EtOAc)

C= (silica gel, EtOAc / hexane 1:1)

5

General working method V (reductive amination):

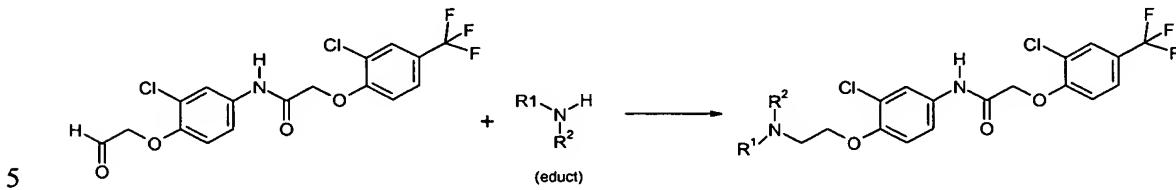
Conc. hydrochloric acid (2.0 eq.) is added to a solution of the aldehyde (see intermediate product Z3d) (1.0 eq.) and amine (2.0 eq.) in THF or the pH is adjusted to between 4-6 with glacial acetic acid. The mixture is stirred for 10 minutes at RT and then sodium cyanoborohydride (2.0 eq.) in THF or sodium triacetoxyborohydride (2.0 eq.) is added. The reaction mixture is stirred for 30 minutes – 24 hours at RT to 60°C, depending on the amine, before adding sat. aqueous sodium bicarbonate solution. After extraction of the aqueous phase with ether the organic phase is dried over magnesium sulphate. The solvent is

10

15

removed using the rotary evaporator; further purification is carried out by column chromatography or crystallisation.

According to general working method V the following compounds were prepared:



while in the Table that follows the products are defined by means of the group $\text{R}^1\text{R}^2\text{N}-$ and the associated educts are commercially available or known from the literature.

Examp le	$\text{R}^1\text{R}^2\text{N}-$	Empirical formula	Mass spectrum	R_f value	Yield (%)
88		$\text{C}_{21}\text{H}_{21}\text{Cl}_2\text{F}_3\text{N}_2\text{O}_3$	477/479/481 [$\text{M}+\text{H}]^+$	0.13 (A)	27
89		$\text{C}_{22}\text{H}_{25}\text{Cl}_2\text{F}_3\text{N}_2\text{O}_3$	493/495/497 [$\text{M}+\text{H}]^+$	0.26 (B)	8
90		$\text{C}_{20}\text{H}_{21}\text{Cl}_2\text{F}_3\text{N}_2\text{O}_3$	465/67/69 [$\text{M}+\text{H}]^+$	0.25 (B)	4
91		$\text{C}_{24}\text{H}_{28}\text{Cl}_2\text{F}_3\text{N}_3\text{O}_3$	534/536 [$\text{M}+\text{H}]^+$	0.10 (B)	30
92		$\text{C}_{20}\text{H}_{21}\text{Cl}_2\text{F}_3\text{N}_2\text{O}_3$	465/467/469 [$\text{M}+\text{H}]^+$	0.28 (B)	9
93		$\text{C}_{26}\text{H}_{25}\text{Cl}_2\text{F}_3\text{N}_2\text{O}_3$	541/543/545 [$\text{M}+\text{H}]^+$	0.80 (B)	10
94		$\text{C}_{26}\text{H}_{23}\text{Cl}_2\text{F}_3\text{N}_2\text{O}_3$	539/541/543 [$\text{M}+\text{H}]^+$	0.35 (B)	19

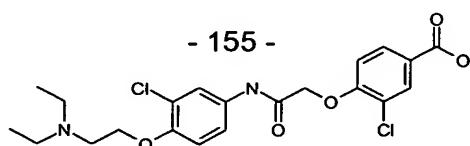
95		C ₂₂ H ₂₅ Cl ₂ F ₃ N ₂ O ₄	509/511/513 [M+H] ⁺	0.37 (B)	7
96		C ₂₃ H ₂₈ Cl ₂ F ₃ N ₃ O ₃	522/524/526 [M+H] ⁺	0.18 (B)	8
97		C ₂₉ H ₃₆ Cl ₂ F ₃ N ₃ O ₅	634/636/638 [M+H] ⁺	0.32 (B)	6
98		C ₂₄ H ₂₁ Cl ₂ F ₃ N ₂ O ₃	513/515/517 [M+H] ⁺	0.47 (C)	27
99		C ₂₅ H ₂₉ Cl ₂ F ₃ N ₂ O ₃	533/535/537 [M+H] ⁺	0.37 (C)	1
100		C ₂₁ H ₂₁ Cl ₂ F ₃ N ₂ O ₄	493/495 [M+H] ⁺	0.33 (B)	13
101		C ₂₅ H ₂₄ Cl ₂ F ₃ N ₃ O ₃	542/544/546 [M+H] ⁺	0.35 (B)	10
102		C ₂₂ H ₂₄ Cl ₂ F ₃ N ₃ O ₃	506/508/510 [M+H] ⁺	0.15 (B)	1
103		C ₂₆ H ₃₀ Cl ₂ F ₃ N ₃ O ₅	592/594/596 [M+H] ⁺	0.55 (B)	21
104		C ₂₉ H ₂₉ Cl ₂ F ₃ N ₂ O ₃	581/583/585 [M+H] ⁺	0.55 (B)	18
105		C ₂₃ H ₂₇ Cl ₂ F ₃ N ₂ O ₃	507/509/511 [M+H] ⁺	0.65 (B)	6

Eluant: A) dichloromethane / MeOH / conc. aqueous ammonia = 95:5:0.5

B) dichloromethane / MeOH / conc. aqueous ammonia = 90:10:1

C) dichloromethane / MeOH = 9:1

Example 106:



106) 3-chloro-4-{{[3-chloro-4-(2-diethylamino-ethoxy)-phenylcarbamoyl]-methoxy}-benzoic acid}

A solution of 1.8 g (3.835 mmol) of methyl 3-chloro-4-{{[3-chloro-4-(2-diethylamino-

5 ethoxy)-phenylcarbamoyl]-methoxy}-benzoate (from Example 35) and 2 ml of 2 M aqueous NaOH solution in 20 mL MeOH was refluxed for 1 hour. The reaction solution was evaporated down i. vac., diluted with water and acidified weakly with HCl. After 3 days at RT the solution was evaporated down i. vac. The residue was triturated with cold EtOH and the precipitate was filtered off.

10 Yield: 230 mg (13 % of theory)

$C_{21}H_{24}Cl_2N_2O_5$ ($M = 455.342$)

Calc.: Molpeak($M+H$) $^+$: 454/456/458

Found: Molpeak ($M+H$) $^+$: 454/456/458 (Cl_2)

R_f value: 0.05 (silica gel, dichloromethane / MeOH / conc. aqueous ammonia

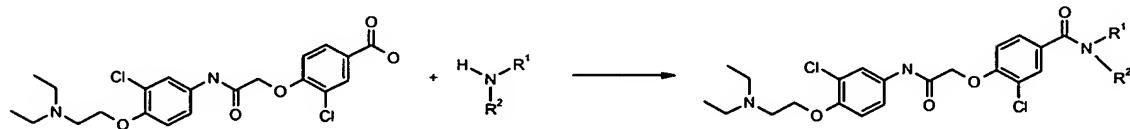
15 90:10:1).

General working method VI:

A solution of 1.0 eq. of 3-chloro-4-{{[3-chloro-4-(2-diethylamino-ethoxy)-

20 phenylcarbamoyl]-methoxy}-benzoic acid (from Example 106) and 1.07 eq. of TBTU in DMF is placed at RT. After the addition of 1.07 eq. triethylamine the mixture is stirred for 10 minutes. Then 7.0 eq. amine are added and the mixture is stirred for 16 hours at RT. The reaction mixture is combined with water or 5% sodium carbonate solution. The precipitated solid is filtered off, washed with water and dried i. vac.

25 According to general working method VI the following compounds were prepared:



while in the Table that follows the products are defined by means of the group R¹R²N- and the associated educts are commercially available or known from the literature.

5

Example	R ¹ R ² N-	Empirical formula	Mass spectrum	R _f value	Yield (%)
107	 aus (NH ₄) ₂ CO ₃	C ₂₁ H ₂₅ Cl ₂ F ₃ N ₃ O ₄	454/456/458 [M+H] ⁺	0.37 (A)	59
108		C ₂₂ H ₂₇ Cl ₂ F ₃ N ₃ O ₄	468/470/472 [M+H] ⁺	0.38 (A)	57
109		C ₂₃ H ₂₉ Cl ₂ F ₃ N ₃ O ₄	482/484/486 [M+H] ⁺	0.38 (A)	55

Eluant: A) dichloromethane / MeOH / conc. aqueous ammonia = 90:10:1

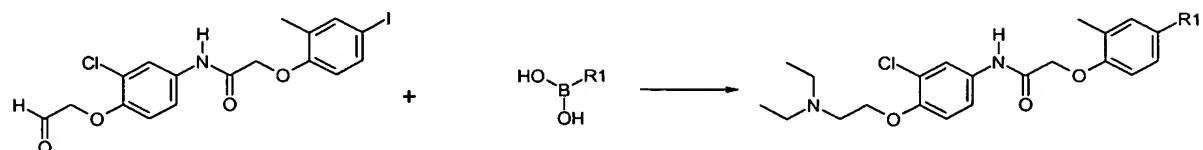
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General working method VII (Suzuki coupling):

Boric acid (2.0 eq.) and tetrakis-(triphenylphosphine)-palladium (0.1 eq.) are added successively to a solution of the iodide (1.0 eq.; see Example 56) in toluene 15 and 2M sodium carbonate solution (4.0 eq.) and stirred overnight at 80°C. The reaction solution is combined with 10 % aqueous Na₂CO₃ solution and the aqueous phase is extracted with EtOAc. The organic phases are combined and the solvent is eliminated in vacuo. Further purification is carried out by column chromatography.

20

According to general working method VII the following compounds were prepared:



5

while in the Table that follows the products are defined by means of the group R1 and the associated educts are commercially available or known from the literature.

Example le	R1	Empirical formula	Mass spectrum	R _f value	Yield (%)
110		C ₂₇ H ₃₀ Cl ₂ N ₂ O ₃	501/503/505 [M+H] ⁺	0.30 (A)	4
111		C ₂₇ H ₃₀ Cl ₂ N ₂ O ₃	501/503/505 [M+H] ⁺	0.30 (A)	4
112		C ₂₇ H ₃₀ Cl ₂ N ₂ O ₃	501/503/505 [M+H] ⁺	0.30 (A)	6
113		C ₂₈ H ₃₃ ClN ₂ O ₄	497/499/501 [M+H] ⁺	0.27 (A)	8
114		C ₂₈ H ₃₃ ClN ₂ O ₄	481/483 [M+H] ⁺	0.6 (B)	21

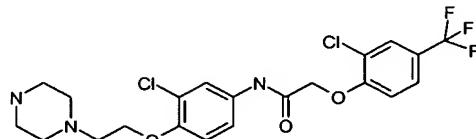
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Eluant: A) dichloromethane / MeOH / conc. aqueous ammonia = 90:10:1
B) EtOAc / MeOH / conc. aqueous ammonia = 90:10:1

Example 115:

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115) N-[3-chloro-4-(2-piperazin-1-yl-ethoxy)-phenyl]-2-(2-chloro-4-trifluoromethyl-



phenoxy)-acetamide

0.200 g (0.338 mmol) of *tert*.butyl 4-(2-chloro-4-[2-(2-chloro-4-trifluoromethyl-phenoxy)-acetyl amino]-phenoxy)-ethyl)-piperazin-1-carboxylate (from Example

5 103) were dissolved in 5.0 mL dichloromethane. After the addition of 0.5 mL
 (6.760 mmol) of trifluoroacetic acid the mixture was stirred for 2 hours at RT. The reaction solution was evaporated down i. vac. and the residue combined with sat. aqueous sodium hydrogen carbonate solution. The aqueous phase was extracted with EtOAc. The org. phase was dried over magnesium sulphate, filtered and
 10 evaporated down i. vac. Further purification was carried out by column chromatography.

Yield: 0.032 g (16 % of theory)

$C_{21}H_{22}Cl_2F_3N_3O_3 * 2 CH_2O_2$ ($M= 584.381$)

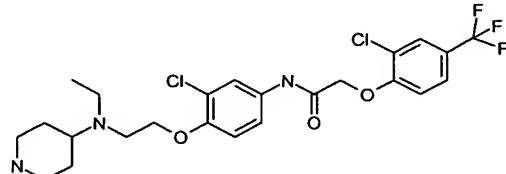
Calc.: Molpeak($M+H$) $^+$: 492/494/496 (Cl_2)

15 Found: Molpeak ($M+H$) $^+$: 492/494/496 (Cl_2)

R_f value: 0.22 (silica gel, dichloromethane / MeOH / conc. aqueous ammonia

90:10:1).

Example 116:



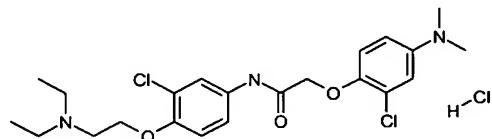
20

116) N-[3-chloro-4-[2-(ethyl-piperidin-4-yl-amino)-ethoxy]-phenyl]-2-(2-chloro-4-trifluoromethyl-phenoxy)-acetamide

0.180 g (0.284 mmol) of *tert*.butyl 4-[(2-{2-chloro-4-[2-(2-chloro-4-trifluoromethyl-phenoxy)-acetylamino]-phenoxy}-ethyl)-ethyl-amino]-piperidine-1-carboxylate (from Example 97) were dissolved in 5.0 mL dichloromethane. After the addition of 0.44 mL (5.680 mmol) of trifluoroacetic acid the mixture was stirred for 2 hours at 5 RT. The reaction solution was evaporated down i. vac. and the residue combined with sat. aqueous sodium hydrogen carbonate solution. The aqueous phase was extracted with EtOAc. The org. phase was dried over magnesium sulphate, filtered and evaporated down i. vac. Further purification was carried out by column chromatography.

10 Yield: 0.011 g (6 % of theory)
 $C_{24}H_{28}Cl_2F_3N_3O_3 * 2 CH_2O_2$ ($M= 626.462$)
 Calc.: Molpeak($M+H$) $^+$: 534/536/538 (Cl_2)
 Found: Molpeak ($M+H$) $^+$: 534/536/538 (Cl_2)
 R_f value: 0.25 (silica gel, dichloromethane / MeOH / conc. aqueous ammonia
 15 90:10:1).

Example 117:



117) N-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-2-(2-chloro-4-dimethylamino-phenoxy)-acetamide
 20 94.7 mg (0.200 mmol) of 2-(4-amino-2-chloro-phenoxy)-N-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-acetamide (from Example 118), 0.149 mL (37%, 2.000 mmol) of formaldehyde solution and 62.8 mg (1.000 mmol) of sodium cyanoborohydride was placed in 5.0 mL acetonitrile at RT. The pH was adjusted to 25 4-5 with glacial acetic acid with stirring. After 1 hour the reaction mixture was acidified with 12 % HCl and stirred for 10 minutes. Then it was made slightly alkaline with 20 % potassium carbonate solution. The aqueous phase was

extracted with EtOAc. The org. phase was dried over magnesium sulphate, filtered and evaporated down i. vac. The residue was purified by column chromatography (silica gel; EtOAc / 10 % conc. aqueous ammonia in MeOH 100:0 → 5:95). The oily residue was combined with ethereal HCl, evaporated down i. vac. and
 5 dissolved in 10 mL isopropanol. The precipitate formed was filtered off and dried i. vac.

Yield: 0.035 g (36 % of theory)

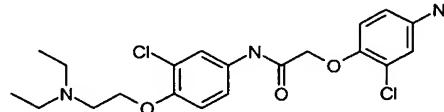
$C_{22}H_{29}Cl_2N_3O_3 \cdot HCl$ ($M= 490.862$)

Calc.: Molpeak($M+H$) $^+$: 454/456/458 (Cl_2)

10 Found: Molpeak ($M+H$) $^+$: 454/456/458 (Cl_2)

R_f value: 0.40 (silica gel, dichloromethane / MeOH / conc. aqueous ammonia 90:10:1)

Example 118:



15

118) 2-(4-amino-2-chloro-phenoxy)-N-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-acetamide

0.310 g (0.679 mmol) of N-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-2-(2-chloro-4-nitro-phenoxy)-acetamide (from Example 66) was dissolved in 10.0 mL of

20 EtOAc. After the addition of 0.030 g Pt/C (5%) the mixture was hydrogenated at RT under 15 psi H_2 atmosphere for 5 hours. The reaction mixture was filtered and the filtrate was evaporated down i. vac. The residue was dissolved with a little EtOH. The precipitate formed was filtered off and dried i. vac.

Yield: 0.050 g (17 % of theory)

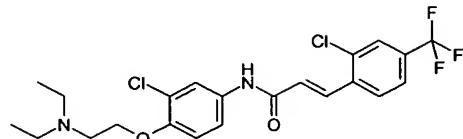
25 $C_{20}H_{25}Cl_2N_3O_3$ ($M= 426.347$)

Calc.: Molpeak($M+H$) $^+$: 426/428/430 (Cl_2)

Found: Molpeak ($M+H$) $^+$: 426/428/430 (Cl_2)

R_f value: 0.24 (silica gel, dichloromethane / MeOH / conc. aqueous ammonia 90:10:1).

Example 119:



5

119) (E)-N-[3-chloro-4-(2-diethylaminoethoxy)-phenyl]-3-(2-chloro-4-trifluoromethyl-phenyl)-acrylamide

0.29 mL (2.10 mmol) of triethylamine was added to a solution of 0.28 g (1.00 mmol) of 3-chloro-4-(2-diethylaminoethoxy)-phenylamine-hydrochloride

10 (intermediate product Z1b), 0.25 g (1.00 mmol) of (E)-3-(2-chloro-4-trifluoromethyl-phenyl)-acrylic acid (Z37b) and 0.34 g (1.05 mmol) of TBTU in 10 mL abs. THF and the mixture was stirred for 1 hour at RT. The reaction mixture was evaporated down i. vac. and the residue was combined with dichloromethane and water. The org. phase was separated off, washed with sat. aqueous sodium bicarbonate solution and water and evaporated down i. vac. The residue was purified by column chromatography (silica gel, gradient dichloromethane / 10 % conc. aqueous ammonia in MeOH 100:0 → 5:95).

Yield: 150 mg (32 % of theory)

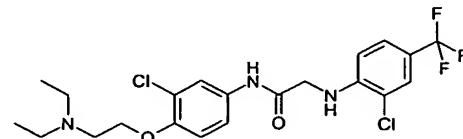
$C_{22}H_{23}Cl_2F_3N_2O_2$ ($M= 475.342$)

20 Calc.: Molpeak($M+H$) $^+$: 475/477/479

Found: Molpeak ($M+H$) $^+$: 475/477/479 (Cl_2)

R_f value: 0.2 (silica gel, dichloromethane / MeOH / conc. aqueous ammonia 95:5:1)

25 Example 120:



120) N-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-2-(2-chloro-4-trifluoromethyl-phenylamino)-acetamide

A solution of 0.228 g (0.511 mmol) of 2-bromo-N-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-acetamide-hydrobromide (intermediate product Z1c) and 0.200 g (1.023 mmol) of 2-chloro-4-trifluoromethyl-phenylamine in 5 mL DMF was stirred for 16 hours at 90 °C and then for 24 hours at 120 °C. The reaction mixture was cooled to RT, diluted with water and exhaustively extracted with EtOAc. The combined org. extracts were dried over magnesium sulphate and evaporated down i. vac. The residue was dissolved in DMF and purified by HPLC-MS (Stable Bond C18; 3.5 µm; water:acetonitrile:formic acid 9:1:0.01 → 1:9:0.01 over 9 min). Yield: 11 mg (5 % of theory)

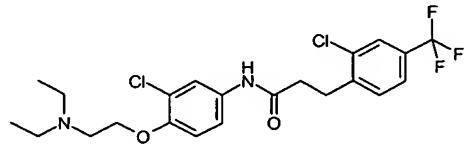
$C_{21}H_{24}Cl_2F_3N_3O_2$ ($M= 478.346$)

Calc.: Molpeak($M+H$)⁺: 478/480/482

15 Found: Molpeak ($M+H$)⁺: 478/480/482 (Cl_2)

R_f value: 0.24 (silica gel, dichloromethane / MeOH / conc. aqueous ammonia 90:10:1).

20 Example 121:



121a) 3-(2-chloro-4-trifluoromethyl-phenyl)-propionic acid

2.00 g (7.981 mmol) of (E)-3-(2-chloro-4-trifluoromethyl-phenyl)-acrylic acid (Z37b) was added at RT to a suspension of 0.500 g Raney nickel in abs. MeOH and the mixture was hydrogenated for 4 hours at 50 psi H_2 atmosphere. The catalyst was filtered off and the filtrate evaporated down i. vac.

Yield: 1.90 g (94 % of theory)

$C_{10}H_8ClF_3O_2$ ($M = 252.622$)

Calc.: Molpeak($M-H^-$): 251/253

Found: Molpeak ($M+H^+$): 251/253 (Cl)

5 121b) N-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-3-(2-chloro-4-trifluoromethyl-phenyl)-propionamide

The product was obtained analogously to Example 119 starting from 0.400 g (1.433 mmol) of 3-chloro-4-(2-diethylamino-ethoxy)-phenylamine-hydrochloride (intermediate product Z1b) and 0.362 g (1.433 mmol) of 3-(2-chloro-4-

10 trifluoromethyl-phenyl)-propionic acid.

Yield: 340 mg (50% of theory)

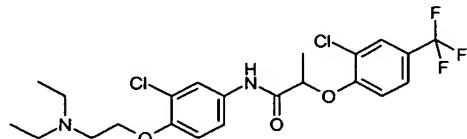
$C_{22}H_{25}Cl_2F_3N_2O_2$ ($M = 477.358$)

Calc.: Molpeak($M-H^-$): 477/479/481

Found: Molpeak ($M+H^+$): 477/479/481 (Cl₂)

15 R_f value: 0.30 (silica gel, dichloromethane / MeOH / conc. aqueous ammonia 90:10:1)

Example 122:



20

122a) ethyl 2-(2-chloro-4-trifluoromethyl-phenoxy)-propionate

10.00 g (50.87 mmol) of 2-chloro-4-trifluoromethyl-phenol, 7.11 mL (55.00 mmol) of ethyl 2-bromopropionate and 7.60 g (55 mmol) of potassium carbonate in 100 mL DMF was stirred for 16 hours at 50 °C and then filtered. The filtrate was

25 evaporated down i. vac., combined with water and exhaustively extracted with EtOAc. The combined org. extracts were washed with 10% aqueous sodium

carbonate solution and water, dried over sodium sulphate and evaporated down i. vac.

Yield: 14.10 g (93 % of theory)

$C_{12}H_{12}ClF_3O_3$ ($M= 296.676$)

5 Calc.: Molpeak($M+Na$) $^+$: 319/321

Found: Molpeak ($M+Na$) $^+$: 319/321 (Cl)

R_f value: 0.6 (silica gel, EtOAc / petroleum ether 4:1)

122b) 2-(2-chloro-4-trifluoromethyl-phenoxy)-propionic acid

10 50 mL (0.100 mol) of 2 M aqueous NaOH solution was added to a solution of 14.00 g (0.047 mol) of ethyl 2-(2-chloro-4-trifluoromethyl-phenoxy)-propionate in 100 mL EtOH and the mixture was refluxed for 1 hour. EtOH was evaporated off i. vac., the residue was diluted with ice water and acidified with 2 M aqueous HCl. The precipitate formed was filtered off, washed with water and dried at 70 °C i.

15 vac.

Yield: 12.10 g (96 % of theory)

$C_{10}H_8ClF_3O_3$ ($M= 268.622$)

Calc.: Molpeak($M-H$) $^-$: 267/269

Found: Molpeak ($M-H$) $^-$: 267/269 (Cl)

20

122c) N-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-2-(2-chloro-4-trifluoromethyl-phenoxy)-propionamide-hydrochloride

0.342 mL (2.000 mmol) of ethyl-diisopropylamine was added to a solution of 0.364 g (1.500 mmol) of 3-chloro-4-(2-diethylamino-ethoxy)-phenylamine (intermediate

25 product Z1b), 0.403 g (1.500 mmol) of 2-(2-chloro-4-trifluoromethyl-phenoxy)-propionic acid and 0.562 g (1.750 mmol) of TBTU in 10 mL abs. THF and the mixture was stirred for 1 hour at RT. The reaction mixture was evaporated down i. vac. and the residue combined with dichloromethane and water. The org. phase was separated off, washed with sat. aqueous sodium bicarbonate solution and water and evaporated down i. vac. The residue was purified by column

chromatography (silica gel, gradient dichloromethane / 10 % conc. aqueous ammonia in MeOH 100:0 → 5:95).

Yield: 450 mg (57 % of theory)

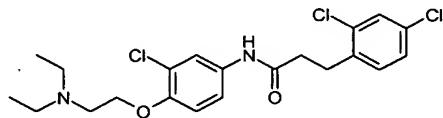
$C_{22}H_{25}Cl_2F_3N_2O_3 \cdot HCl$ ($M= 529.818$)

5 Calc.: Molpeak($M+H$) $^+$: 493/495/497

Found: Molpeak ($M+H$) $^+$: 493/495/497 (Cl_2)

R_f value: 0.30 (silica gel, dichloromethane / MeOH / conc. aqueous ammonia 95:5:0.5).

10 Example 123:



123) N-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-3-(2,4-dichloro-phenyl)-propionamide

A solution of 0.271 g (1.236 mmol) of (3-(2,4-dichloro-phenyl)-propionic acid in 15 3.00 mL thionyl chloride was stirred for 2 hours at RT, evaporated down i. vac. and dissolved in 10 mL dichloromethane. This solution of the acid chloride was slowly added dropwise, while cooling with ice, to a solution of 0.300 (1.236 mmol) of 3-chloro-4-(2-diethylamino-ethoxy)-phenylamine (intermediate product Z1b) and 0.32 mL (1.854 mmol) of ethyl-diisopropylamine in 10 mL dichloromethane and the 20 mixture was stirred for 16 hours at RT. The reaction mixture was washed with sat. aqueous sodium bicarbonate solution, dried over magnesium sulphate and evaporated down i. vac. The residue was dissolved in EtOAc and purified by column chromatography (silica gel, EtOAc / MeOH / conc. aqueous ammonia 90:10:1).

25 Yield: 60 mg (11 % of theory)

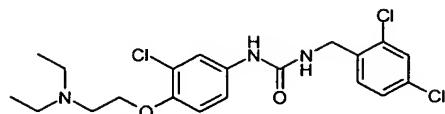
$C_{21}H_{25}Cl_3N_2O_2$ ($M= 443.$)

Calc.: Molpeak($M-Na$) $^+$: 441/443/445

Found: Molpeak ($M-Na$) $^+$: 441/443/445 (Cl_2)

R_f value: 0.27 (silica gel, dichloromethane / MeOH / conc. aqueous ammonia 90:10:1)

5 Example 124:



124) 1-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-3-(2,4-dichloro-benzyl)-urea

203 mg (1.236 mmol) of CDT in 4 mL DMF was added to a solution of 345 mg (1.236 mmol) of 3-chloro-4-(2-diethylamino-ethoxy)-phenylamine-hydrochloride

10 (intermediate product Z1b) and 0.56 mL (4.000 mmol) of triethylamine in 40 mL THF and the mixture was stirred for 2 hours at RT. 176 mg (1.236 mmol) of 2,4-dichloro-benzylamine was added, the reaction mixture was refluxed for 4 hours and then evaporated down i. vac. The residue was purified by column chromatography (silica gel, dichloromethane / MeOH / conc. aqueous ammonia 80:20:1) and the product was triturated with diisopropylether.

Yield: 300 mg (55 % of theory)

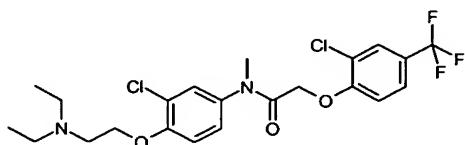
$C_{20}H_{24}Cl_3N_3O_2$ ($M = 444.792$)

Calc.: Molpeak($M+H$)⁺: 444/446/448

Found: Molpeak ($M+H$)⁺: 444/446/448 (Cl_3)

20 R_f value: 0.73 (silica gel, dichloromethane / MeOH / conc. aqueous ammonia 80:20:1)

Example 125:



125a) tert.butyl [3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-carbaminate
0.31 mL (2.266 mmol) of triethylamine was added to a solution of 0.500 g (2.06
mmol) of 3-chloro-4-(2-diethylamino-ethoxy)-phenylamine and 0.495 g (2.266
5 mmol) of Boc-anhydride in 10 mL dichloromethane at RT and the mixture was
stirred for 48 hours. The reaction mixture was diluted with dichloromethane and
the org. phase was washed with sat. aqueous sodium bicarbonate solution. The
combined org. extracts were dried over magnesium sulphate and evaporated
down i. vac. Column chromatography (silica gel, dichloromethane / MeOH / conc.
10 aqueous ammonia 90:10:1) yielded the product.

Yield: 500 mg (71 % of theory)

$C_{17}H_{27}ClN_2O_3$ ($M= 342.869$)

Calc.: Molpeak($M+H^+$): 343/345

Found: Molpeak ($M+H^+$): 343/345 (Cl)

15
125b) [3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-methyl-amine
Under a nitrogen atmosphere a solution of 500 mg (1.458 mmol) of tert.butyl [3-
chloro-4-(2-diethylamino-ethoxy)-phenyl]-carbaminate in 10 mL THF was slowly
added dropwise to a suspension of 165 mg (4.374 mmol) of lithium aluminium
20 hydride in 20 mL abs. THF and the mixture was stirred for 16 hours at RT. 165 μ L
of water, 165 μ L of 15% aqueous NaOH solution and a further 495 μ L water was
added and the precipitate formed was filtered off. The filtrate was dried over
magnesium sulphate, evaporated down i. vac. and the residue was purified by
column chromatography (silica gel, EtOAc / MeOH / conc. aqueous ammonia
25 90:10:1).

Yield: 180 mg (48 % of theory)

$C_{13}H_{21}ClN_2O$ ($M= 256.778$)

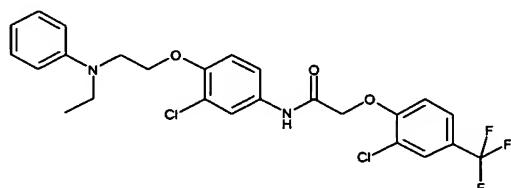
Calc.: Molpeak($M+H^+$): 257/259

Found: Molpeak ($M+H^+$): 257/259 (Cl)

30 R_f value: 0.61 (silica gel, EtOAc / MeOH / conc. aqueous ammonia 90:10:1)

125c) N-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-2-(2-chloro-4-trifluoromethyl-phenoxy)-N-methyl-acetamide

293 mg (0.911 mmol) of TBTU and 123 mg (0.911 mmol) of HOBT were added to
 5 a suspension of 231 mg (0.911 mmol) of (2-chloro-4-trifluoromethyl-phenoxy)-
 acetic acid (intermediate product Z2b) in 5 mL abs. THF and the mixture was
 stirred for 10 minutes at RT. 180 mg (0.701 mmol) of [3-chloro-4-(2-diethylamino-
 ethoxy)-phenyl]-methyl-amine and 0.18 mL (1.051 mmol) of ethyl-diisopropylamine
 were added, the mixture was stirred for 16 hours at RT and evaporated down i.
 10 vac. The residue was purified by column chromatography (silica gel, silica gel,
 dichloromethane / MeOH / conc. aqueous ammonia 85:15:1).
 Yield: 150 mg (43 % of theory)
 $C_{22}H_{25}Cl_2F_3N_2O_3$ ($M= 493.357$)
 Calc.: Molpeak($M+H$) $^+$: 493/495/497
 15 Found: Molpeak ($M+H$) $^+$: 493/495/497 (Cl_2)
 R_f value: 0.416 (silica gel, dichloromethane / MeOH / conc. aqueous ammonia
 90:10:1).



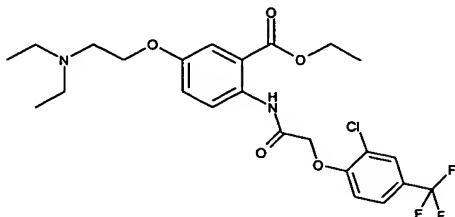
Example 126:

126) N-[3-chloro-4-[2-(ethyl-phenyl-amino)-ethoxy]-phenyl]-2-(2-chloro-4-trifluoromethyl-phenoxy)-acetamide
 20 The product was obtained according to general working method V starting from 0.422 g (0.616 mmol) N-[3-chloro-4-(2-oxo-ethoxy)-phenyl]-2-(2-chloro-4-trifluoromethyl-phenoxy)-acetamide (Z3d) and 0.094 mL (0.739 mmol) N-ethylaniline.
 25 Yield: 20 mg (6.2% of theory)
 $C_{25}H_{23}Cl_2F_3N_2O_3$ ($M= 527.375$)
 Calc.: molpeak ($M-H$) $^-$: 525/527/529

Found: molpeak (M-H)⁻: 525/527/529 (Cl₂)

R_f value: 0.94 (silica gel, EtOAc)

Example 127:



5

ethyl 2-[2-(2-chloro-4-trifluoromethyl-phenoxy)-acetylamino]-5-(2-diethylaminoethoxy)-benzoate

The product was obtained according to general working method I starting from 1.00 g (3.567 mmol) (2-chloro-4-trifluoromethyl-phenoxy)-acetic acid (Z2b) and 10 0.908 g (3.567 mmol) ethyl 2-amino-5-(2-diethylaminoethoxy)-benzoate (Z25c).

Yield: 1.700 g (92% of theory)

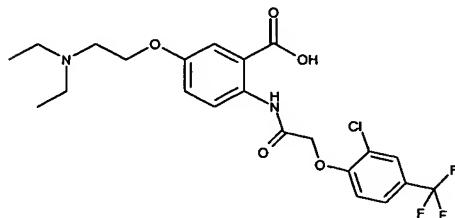
C₂₄H₂₈ClF₃N₂O₅ (M= 516.949)

Calc.: molpeak (M-H)⁻: 515/517

Found: molpeak (M-H)⁻: 515/517 (Cl⁻)

15 R_f value: 0.35 (silica gel, EtOAc / MeOH / conc. aqueous ammonia 90:10:1).

Example 128:



128) 2-[2-(2-chloro-4-trifluoromethyl-phenoxy)-acetylamino]-5-(2-diethylamino-

20 ethoxy)-benzoic acid

10 mL aqueous NaOH (1N) was added to a solution of 0.900 g (1.741 mmol) ethyl 2-[2-(2-chloro-4-trifluoromethyl-phenoxy)-acetylamino]-5-(2-diethylaminoethoxy)-benzoate (Example 127) in 30 mL EtOH and the mixture was stirred for 2 h at RT.

The reaction mixture was acidified with 10 mL aqueous HCl (1M) and treated with ultrasound for 30 min.. The precipitate was filtered off, washed with water and dried at 50 °C i. vac..

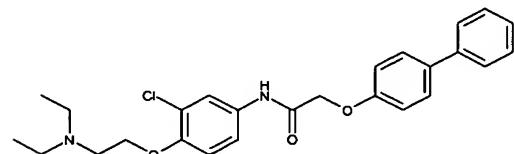
Yield: 0.640 g (75% of theory)

5 C₂₂H₂₄ClF₃N₂O₅ (M= 488.895)

Calc.: molpeak (M-H)⁺: 487/489

Found: molpeak (M-H)⁺: 487/489 (Cl)

Example 129:



10

129) 2-(biphenyl-4-yloxy)-N-[3-chloro-4-(2-diethylaminoethoxy)-phenyl]-acetamide

The product was prepared according to general working method I from (biphenyl-4-yloxy)-acetic acid and 3-chloro-4-(2-diethylaminoethoxy)-phenylamine.

Yield: 0.560 g (58% of theory)

15

C₂₆H₂₉ClN₂O₃ (M= 452.986)

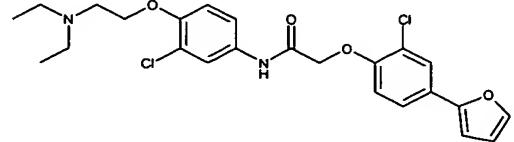
Calc.: molpeak (M+H)⁺: 453/455

Found: molpeak (M+H)⁺: 453/455 (Cl)

R_f value: 0.76 (silica gel, dichloromethane / MeOH / cyclohexane / conc. aqueous ammonia 75:15:15:1).

20

Example 130:



130a) ethyl (2-chloro-4-furan-2-yl-phenoxy)-acetate

3.5 mL aqueous sodium carbonate solution (1 M) was added to a solution of 1.00

25

g (3.407 mmol) ethyl (4-bromo-2-chloro-phenoxy)-acetate (Z26), 0.784 g (6.800 mmol) 2-furanboric acid and 0.196 g (0.170 mmol) tetrakis-triphenylphosphine-

palladium in 65 mL dioxane and the mixture was refluxed for 4 h. The reaction mixture was cooled to RT, evaporated down i. vac. , diluted with water and exhaustively extracted with EtOAc. The combined org. phases were washed with saturated aqueous sodium bicarbonate, water and saturated aqueous NaCl, dried

5 over sodium sulphate and evaporated down i. vac. . Column chromatography (silica gel, petroleum ether / EtOAc 3:1) yielded the product.

Yield: 0.800 g (84% of theory)

$C_{14}H_{13}ClO_4$ ($M= 280.710$)

Calc.: molpeak ($M+H^+$): 281/283

10 Found: molpeak ($M+H^+$): 281/283 (Cl)

R_f value: 0.56 (silica gel, petroleum ether / EtOAc 3:1).

130b) (2-chloro-4-furan-2-yl-phenoxy)-acetic acid

0.40 g (10.00 mmol) NaOH in 5 mL water was added to a solution of 0.280 g

15 (2.672 mmol) ethyl (2-chloro-4-furan-2-yl-phenoxy)-acetate (130a) in 20 mL abs. EtOH and the mixture was stirred for 16 h at RT. The reaction mixture was diluted with water and acidified to pH 1 with semiconc. aqueous HCl. The precipitate was filtered off, washed with water and dried in a HV.

Yield: 0.630 g (93% of theory)

20 $C_{12}H_9ClO_4$ ($M= 252.656$)

Calc.: molpeak ($M-H^-$): 251/253

Found: molpeak ($M-H^-$): 251/253 (Cl)

130c) N-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-2-(2-chloro-4-furan-2-yl-

25 phenoxy)-acetamide

The product was prepared according to general working method I from 2-chloro-4-furan-2-yl-phenoxy)-acetic acid (130b) and 3-chloro-4-(2-diethylamino-ethoxy)-phenylamine (Z1b).

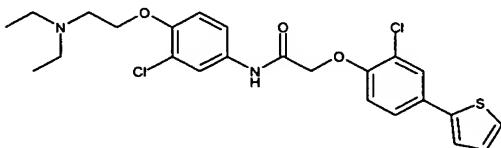
Yield: 0.380 g (79% of theory)

30 $C_{24}H_{26}Cl_2N_2O_4$ ($M= 477.392$)

Calc.: molpeak ($M+H^+$): 477/479/481

Found: molpeak ($M+H$)⁺: 477/479/481 (Cl₂)
 R_f value: 0.70 (Alox, dichloromethane / MeOH 30:1).

Example 131:



5

131a) ethyl (2-chloro-4-thiophen-2-yl-phenoxy)-acetate

Prepared analogously to Example 130a from ethyl (4-bromo-2-chloro-phenoxy)-acetate (Z26) and thiophene-2-boric acid.

Yield: 0.730 g (72% of theory)

10 C₁₄H₁₃ClO₃S (M= 296.775)

Calc.: molpeak ($M+H$)⁺: 297/299

Found: molpeak ($M+H$)⁺: 297/299 (Cl)

R_f value: 0.60 (silica gel, petroleum ether / EtOAc 3:1).

15 131b) (2-chloro-4-thiophen-2-yl-phenoxy)-acetic acid

Prepared analogously to Example 130b from ethyl (2-chloro-4-thiophen-2-yl-phenoxy)-acetate (131a).

Yield: 0.600 g (95% of theory)

C₁₂H₉ClO₃S (M= 268.721)

20 Calc.: molpeak ($M+H$)⁺: 267/269

Found: molpeak ($M+H$)⁺: 267/269 (Cl)

131c) N-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-2-(2-chloro-4-thiophen-2-yl-phenoxy)-acetamide

25 The product was prepared according to general working method I from 2-chloro-4-thiophen-2-yl-phenoxy)-acetic acid (131b) and 3-chloro-4-(2-diethylamino-ethoxy)-phenylamine (Z1b).

Yield: 0.410 g (83% of theory)

$C_{24}H_{26}Cl_2N_2O_3S$ ($M = 493.456$)

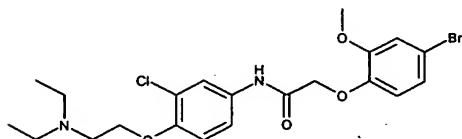
Calc.: molpeak ($M+H$) $^+$: 491/493/495

Found: molpeak ($M+H$) $^+$: 491/493/495 (Cl_2)

R_f value: 0.64 (Alox, dichloromethane / MeOH 30:1).

5

Example 132:



132a) ethyl 2-(4-bromo-2-methoxy-phenoxy)-acetate

Prepared analogously to Intermediate product Z2a from ethyl bromo-acetate and

10 2-methoxy-4-bromophenol.

Yield: 3.600 g (83% of theory)

$C_{11}H_{13}BrO_4$ ($M = 289.128$)

Calc.: molpeak ($M+H$) $^+$: 289/291

Found: molpeak ($M+H$) $^+$: 289/291 (Br).

15

132b) 2-(4-bromo-2-methoxy-phenoxy)-acetic acid

Prepared analogously to Example 130b from ethyl 2-(4-bromo-2-methoxy-phenoxy)-acetate (132a).

Yield: 3.250 g (quant. yield)

20 $C_9H_9BrO_4$ ($M = 289.128$)

Calc.: molpeak ($M+H$) $^+$: 261/263

Found: molpeak ($M+H$) $^+$: 261/263 (Br).

25 132c) 2-(4-bromo-2-methoxy-phenoxy)-N-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-acetamide

The product was prepared according to general working method I from 2-(4-bromo-2-methoxy-phenoxy)-acetic acid (132b) and 3-chloro-4-(2-diethylamino-ethoxy)-phenylamine (Z1b).

Yield: 0.050 g (20% of theory)

$C_{21}H_{26}BrClN_2O_4$ ($M= 485.809$)

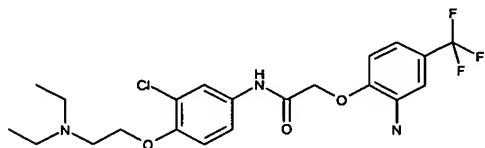
Calc.: molpeak ($M+H$) $^+$: 485/487/489

Found: molpeak ($M+H$) $^+$: 485/487/489 (BrCl)

R_f value: 0.55 (silica gel, dichloromethane / MeOH 9:1).

5

Example 133:



133) 2-(2-amino-4-trifluoromethyl-phenoxy)-N-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-acetamide

10 A suspension of 0.280 g (0.570 mmol) 2-(2-amino-4-trifluoromethyl-phenoxy)-N-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-acetamide (Example 65) and 50 mg Raney nickel in 10 mL MeOH was hydrogenated for 5 h at 50 psi. The catalyst was filtered off and the filtrate evaporated down i. vac. Column chromatography (Alox, N, act. II-III, gradient dichloromethane / MeOH 49:1 → 19:1) yielded the

15 product.

Yield: 0.180 g (69% of theory)

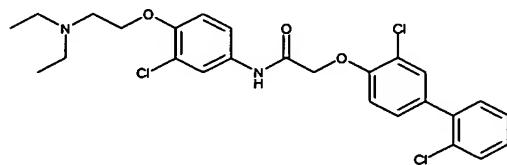
$C_{21}H_{25}ClF_3N_3O_3$ ($M= 459.900$)

Calc.: molpeak ($M+H$) $^+$: 460/462

Found: molpeak ($M+H$) $^+$: 460/462 (Cl)

20 R_f value: 0.42 (Alox, dichloromethane / MeOH 19:1).

Example 134:



25 134a) ethyl (3,2'-dichloro-biphenyl-4-yloxy)-acetate

Prepared analogously to Example 130a from ethyl (4-bromo-2-chloro-phenoxy)-acetate (Z26) and 2-chlorophenylboric acid.

Yield: 1.070 g (97% of theory)

$C_{16}H_{14}Cl_2O_3$ ($M= 325.194$)

5 R_f value: 0.58 (silica gel, petroleum ether / EtOAc 3:1).

134b) (3,2'-dichloro-biphenyl-4-yloxy)-acetic acid

Prepared analogously to Example 130b from ethyl (3,2'-dichloro-biphenyl-4-yloxy)-acetate (134a).

10 Yield: 0.900 g (92% of theory)

$C_{14}H_{10}Cl_2O_3$ ($M= 297.140$)

Calc.: molpeak ($M-H$): 295/297/299

Found: molpeak ($M-H$): 295/297/299 (Cl_2)

15 134c) N-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-2-(3,2'-dichloro-biphenyl-4-yloxy)-acetamide

The product was prepared according to general working method I from (3,2'-dichloro-biphenyl-4-yloxy)-acetic acid (134b) and 3-chloro-4-(2-diethylamino-ethoxy)-phenylamine (Z1b).

20 Yield: 0.250 g (48% of theory)

$C_{26}H_{27}Cl_3N_2O_3$ ($M= 521.876$)

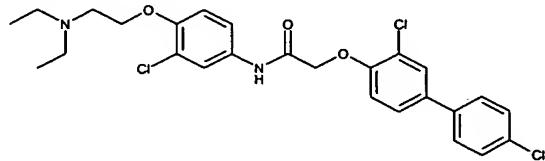
Calc.: molpeak ($M+H$): 521/523/525/527

Found: molpeak ($M+H$): 521/523/525/527 (Cl_3)

R_f value: 0.65 (Alox, dichloromethane / MeOH 30:1).

25

Example 135:



135a) ethyl (3,4'-dichloro-biphenyl-4-yloxy)-acetate

Prepared analogously to Example 130a from ethyl (4-bromo-2-chloro-phenoxy)-acetate (Z26) and 4-chlorophenylboric acid.

Yield: 0.430 g (68% of theory)

5 $C_{16}H_{14}Cl_2O_3$ ($M= 325.194$)

R_f value: 0.62 (silica gel, petroleum ether / EtOAc 3:1).

135b) (3,4'-dichloro-biphenyl-4-yloxy)-acetic acid

Prepared analogously to Example 130b from ethyl (3,4'-dichloro-biphenyl-4-yloxy)-

10 acetate (135a).

Yield: 0.299 g (76% of theory)

$C_{14}H_{10}Cl_2O_3$ ($M= 297.140$)

Calc.: molpeak ($M-H$) $^+$: 295/297/299

Found: molpeak ($M-H$) $^+$: 295/297/299 (Cl_2)

15

135c) N-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-2-(3,4'-dichloro-biphenyl-4-yloxy)-acetamide

The product was prepared according to general working method I from (3,4'-dichloro-biphenyl-4-yloxy)-acetic acid (135b) and 3-chloro-4-(2-diethylamino-

20 ethoxy)-phenylamine (Z1b).

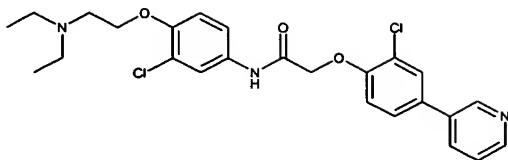
Yield: 0.280 g (60% of theory)

$C_{26}H_{27}Cl_3N_2O_3$ ($M= 521.876$)

Calc.: molpeak ($M+H$) $^+$: 521/523/525/527

Found: molpeak ($M+H$) $^+$: 521/523/525/527 (Cl_3)

25 R_f value: 0.48 (Alox, dichloromethane / MeOH 50:1).

Example 136:

136a) ethyl (2-chloro-4-pyridin-3-yl-phenoxy)-acetate

Prepared analogously to Example 130a from ethyl (4-bromo-2-chloro-phenoxy)-

5 acetate (Z26) and pyridine-3-boric acid.

Yield: 0.420 g (58 % of theory)

$\text{C}_{16}\text{H}_{14}\text{ClNO}_3$ ($M= 291.737$)

R_f value: 0.45 (silica gel, petroleum ether / EtOAc 1:3).

10 136b) (2-chloro-4-pyridin-3-yl-phenoxy)-acetic acid

250 mg (6.250 mmol) NaOH in 10 mL water was added to a solution of 0.400 g (1.371 mmol) ethyl (2-chloro-4-pyridin-3-yl-phenoxy)-acetate in 40 mL abs. EtOH and the mixture was stirred for 1 h at RT. The reaction mixture was acidified with aqueous HCl (1 M) to pH 7.5, the precipitate was filtered off and washed with

15 water.

Yield: 0.269 g (74 % of theory)

$\text{C}_{13}\text{H}_{10}\text{ClNO}_3$ ($M= 263.683$)

Calc.: molpeak ($\text{M}+\text{Na}$) $^+$: 264/266

Found: molpeak ($\text{M}+\text{Na}$) $^+$: 264/266 (Cl_3)

20

136c) N-[3-chloro-4-(2-diethylaminoethoxy)phenyl]-2-(2-chloro-4-pyridin-3-yl-phenoxy)-acetamide

The product was prepared according to general working method I from (2-chloro-4-pyridin-3-yl-phenoxy)-acetic acid (136b) and 3-chloro-4-(2-diethylaminoethoxy)-phenylamine (Z1b).

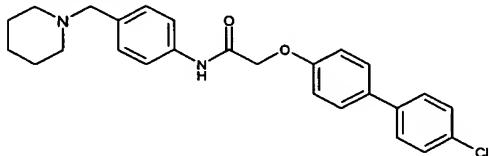
25 Yield: 0.328 g (75% of theory)

$\text{C}_{25}\text{H}_{27}\text{Cl}_2\text{N}_3\text{O}_3$ ($M= 488.418$)

Calc.: molpeak ($\text{M}+\text{H}$) $^+$: 488/490/492

Found: molpeak ($M+H$)⁺: 488/490/492 (Cl₂)
 R_f value: 0.47 (Alox, dichloromethane / MeOH 30:1).

5 Example 137:



137a) (4'-chloro-biphenyl-4-yloxy)-acetic acid

1.5 mL TFA was added to a solution of 0.750 g (2.000 mmol) tert-butyl (4'-chlorobiphenyl-4-yloxy)-acetate in 20 mL dichloromethane and the mixture was stirred

10 for 16 h at RT. The reaction mixture was evaporated down i. vac. and diluted with 1 M aqueous NaOH and EtOAc. The precipitate was filtered off and dried at 80 °C i. vac..

Yield: 0.522 g (quant. yield)

C₁₄H₁₁ClO₃ (M= 262.695)

15 Calc.: molpeak ($M-H$)⁻: 261/263

Found: molpeak ($M-H$)⁻: 261/263 (Cl)

137b) 2-(4'-chlorobiphenyl-4-yloxy)-N-(4-piperidin-1-ylmethyl-phenyl)-acetamide

The product was prepared according to general working method I from (4'-chlorobiphenyl-4-yloxy)-acetic acid (137a) and 4-piperidin-ylmethyl-phenylamine.

Yield: 0.140 g (40% of theory)

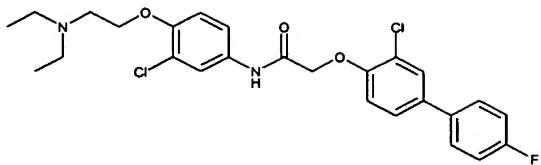
C₂₆H₂₇CIN₂O₂ (M= 434.970)

Calc.: molpeak ($M+H$)⁺: 435/437

Found: molpeak ($M+H$)⁺: 435/437 (Cl)

25 R_f value: 0.40 (silica gel, dichloromethane / MeOH 9:1).

Example 138:



138a) ethyl (3-chloro-4'-fluoro-biphenyl-4-yloxy)-acetate

Prepared analogously to Example 130a from ethyl (4-bromo-2-chloro-phenoxy)-

5 acetate (Z26) and 4-fluoro-phenylboric acid.

Yield: 0.850 g (81% of theory)

$C_{16}H_{14}ClFO_3$ ($M= 308.740$)

Calc.: molpeak ($M+H^+$): 309/311

Found: molpeak ($M+H^+$): 309/311 (Cl)

10 R_f value: 0.45 (silica gel, petroleum ether / EtOAc 3:1).

138b) (3-chloro-4'-fluoro-biphenyl-4-yloxy)-acetic acid

Prepared analogously to Example 130b from ethyl (3-chloro-4'-fluoro-biphenyl-4-yloxy)-acetate (138a).

15 Yield: 0.520 g (67% of theory)

$C_{14}H_{10}ClFO_3$ ($M= 280.685$)

Calc.: molpeak ($M-H^-$): 279/281

Found: molpeak ($M-H^-$): 279/281 (Cl)

20 138c) N-[3-chloro-4-(2-diethylaminoethoxy)phenyl]-2-(3-chloro-4'-fluoro-biphenyl-4-yloxy)-acetamide

The product was prepared according to general working method I from (3-chloro-4'-fluoro-biphenyl-4-yloxy)-acetic acid (138b) and 3-chloro-4-(2-diethylaminoethoxy)-phenylamine (Z1b).

25 Yield: 0.440 g (87% of theory)

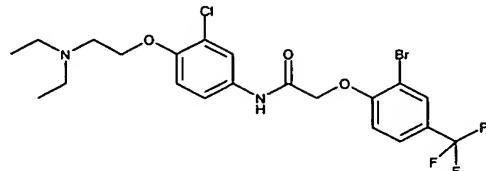
$C_{26}H_{27}Cl_2FN_2O_3$ ($M= 505.421$)

Calc.: molpeak ($M+H^+$): 505/507/509

Found: molpeak ($M+H^+$): 505/507/509 (Cl₂)

R_f value: 0.46 (Alox, dichloromethane / MeOH 50:1).

Example 139:



5

139a) ethyl (2-bromo-4-trifluoromethyl-phenoxy)-acetate

A solution of 2.650 g (11.000 mmol) 2-bromo-4-trifluoromethyl-phenol and 1.47 mL 13.20 mmol) ethyl bromo-acetate in 20 mL Hünig base was stirred for 5 h at 120 °C. The reaction mixture was diluted with EtOAc and the org. phase was washed with water, saturated aqueous sodium bicarbonate and saturated aqueous NaCl, dried over magnesium sulphate and evaporated down i. vac. Column chromatography (silica gel, gradient dichloromethane / MeOH 100:0 → 19:1) yielded the product.

Yield: 2.80 g (78% of theory)

15 $C_{11}H_{10}BrF_3O_3$ ($M=327.100$)

Calc.: molpeak ($M+H$)⁺: 327/329

Found: molpeak ($M+H$)⁺: 327/329 (Br)

R_f value: 0.85 (silica gel, dichloromethane).

20 139b) (2-bromo-4-trifluoromethyl-phenoxy)-acetic acid

Prepared analogously to Example 130b from ethyl (2-bromo-4-trifluoromethyl-phenoxy)-acetate (139a).

Yield: 2.150 g (84% of theory)

$C_9H_6BrF_3O_3$ ($M=299.046$)

25 Calc.: molpeak ($M-H$)⁻: 297/299

Found: molpeak ($M-H$)⁻: 297/299 (Br)

R_f value: 0.35 (silica gel, dichloromethane / MeOH 49:1).

139c) 2-(2-bromo-4-trifluoromethyl-phenoxy)-N-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-acetamide

The product was prepared according to general working method I from (2-bromo-4-trifluoromethyl-phenoxy)-acetic acid (139b) and 3-chloro-4-(2-diethylamino-

5 ethoxy)-phenylamine (Z1b).

Yield: 0.450 g (86% of theory)

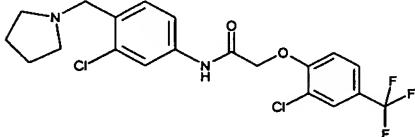
$C_{21}H_{23}BrClF_3N_2O_3$ ($M= 523.781$)

Calc.: molpeak ($M+H$) $^+$: 523/525/527

Found: molpeak ($M+H$) $^+$: 523/525/527 (BrCl)

10 R_f value: 0.45 (silica gel, dichloromethane / MeOH 9:1).

Example 140:



15 140a) 1-(2-chloro-4-nitro-benzyl)-pyrrolidine

10.50 g (74.452 mmol) potassium carbonate was added to a solution of 7.400 g (29.543 mmol) of 1-bromomethyl-2-chloro-4-nitro-benzene and 5.00 mL (59.300 mmol) pyrrolidine in 150 mL acetonitrile and the mixture was stirred for 16 h at RT. The reaction mixture was diluted with 200 mL dichloromethane, filtered and the filtrate evaporated down i. vac. The residue was taken up in EtOAc, the org. phase was washed with water, dried over magnesium sulphate and evaporated down i. vac. The crude product was used in the next reaction step without any further purification.

20 Yield: 6.100 g (86% of theory)

25 $C_{11}H_{13}ClN_2O_2$ ($M= 240.691$)

Calc.: molpeak ($M+H$) $^+$: 241/243

Found: molpeak ($M+H$) $^+$: 241/243 (Cl)

R_f value: 0.38 (silica gel, petroleum ether / EtOAc 2:1).

140b) 3-chloro-4-pyrrolidin-1-ylmethyl-phenylamine

A suspension of 1.00 g (4.155 mmol) 1-(2-chloro-4-nitro-benzyl)-pyrrolidine (140a) and 100 mg Raney nickel in 30 mL MeOH were hydrogenated at RT and 10 psi.

The catalyst was filtered off and the filtrate evaporated down i. vac. .

5 Yield: 0.840 g (96% of theory)

$C_{11}H_{15}ClN_2$ ($M= 210.709$)

Calc.: molpeak ($M+H$) $^+$: 211/213

Found: molpeak ($M+H$) $^+$: 211/213 (Cl)

R_f value: 0.78 (silica gel, dichloromethane / MeOH / cyclohexane / conc. aqueous

10 ammonia 75:15:15:1).

140c) N-(3-chloro-4-pyrrolidin-1-ylmethyl-phenyl)-2-(2-chloro-4-trifluoromethyl-phenoxy)-acetamide

The product was prepared according to general working method I from (2-chloro-4-trifluoromethyl-phenoxy)-acetic acid (Z2b) and 3-chloro-4-pyrrolidin-1-ylmethyl-phenylamine (140b).

Yield: 0.360 g (51% of theory)

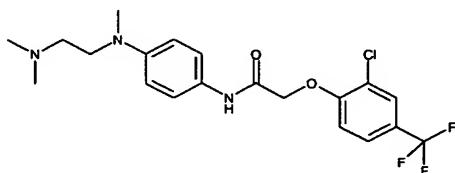
$C_{20}H_{19}Cl_2F_3N_2O_2$ ($M= 447.288$)

Calc.: molpeak ($M+H$) $^+$: 447/449/451

20 Found: molpeak ($M+H$) $^+$: 447/449/451 (Cl_2)

R_f value: 0.58 (silica gel, dichloromethane / EtOAc / MeOH / conc. aqueous ammonia 350:75:75:10).

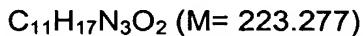
25 Example 141:



141a) N,N,N'-trimethyl-N'-(4-nitro-phenyl)-ethane-1,2-diamine

3.600 g (25.514 mmol) 1-fluoro-4-nitrobenzene and 8.00 mL (62.948 mmol) N,N,N'-trimethyl-ethylene-1,2-diamine were stirred for 1 h at 100 °C and then cooled to RT. The reaction mixture was diluted with water and exhaustively extracted with ether. The combined org. phases were dried over sodium sulphate and evaporated down i. vac. .

Yield: 5.771 g (quant. yield)



Calc.: molpeak (M+H)⁺: 224

Found: molpeak (M+H)⁺: 224

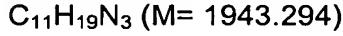
10 R_f value: 0.32 (silica gel, EtOAc / EtOH / conc. aqueous ammonia 50:10:1).

141b) N-(2-dimethylamino-ethyl)-N-methylbenzene-1,4-diamine

A suspension of 5.770 g (25.842 mmol), N,N'-trimethyl-N'-(4-nitro-phenyl)-ethane-1,2-diamine (141a) and 0.60 g Pd/C (10%) in EtOH was hydrogenated for 4.5 h at

15 50 psi. The catalyst was filtered off and the filtrate evaporated down i. vac. . The crude product was further reacted immediately.

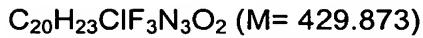
Yield: 3.162 g (63% of theory)



20 141c) 2-(2-chloro-4-trifluoromethyl-phenoxy)-N-{4-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-acetamide

The product was prepared according to general working method I from (2-chloro-4-trifluoromethyl-phenoxy)-acetic acid (Z2b) and N-(2-dimethylamino-ethyl)-N-methylbenzene-1,4-diamine (141b).

25 Yield: 0.110 g (37% of theory)



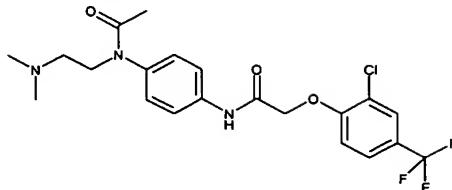
Calc.: molpeak (M+H)⁺: 430/432

Found: molpeak (M+H)⁺: 430/432 (Cl)

R_f value: 0.37 (silica gel, dichloromethane / MeOH / conc. aqueous ammonia

30 90:10:1).

Example 142:



142a) N-(2-dimethylamino-ethyl)-N-(4-nitro-phenyl)-acetamide

5 A solution of 50 g (0.239 mol) N,N-dimethyl-N'-(4-nitro-phenyl)-ethane-1,2-diamine in 500 mL acetic anhydride was stirred for 3.5 h at 130 °C, then evaporated down i. vac. and neutralised with saturated aqueous sodium bicarbonate. The residue was exhaustively extracted with EtOAc, the combined org. phases were dried over sodium sulphate and evaporated down i. vac. .

10 Yield: 58.36 g (97% of theory)
 $C_{12}H_{17}N_3O_3$ (M= 251.288)
 Calc.: molpeak (M+H)⁺: 252
 Found: molpeak (M+H)⁺: 252
 R_f value: 0.55 (silica gel, dichloromethane / MeOH / conc. aqueous ammonia
 15 90:10:1).

142b) N-(4-amino-phenyl)-N-(2-dimethylamino-ethyl)-acetamide

Prepared analogously to Example 141b starting from -(2-dimethylamino-ethyl)-N-(4-nitro-phenyl)-acetamide (142a).

20 Yield: 50.66 g (99% of theory)
 $C_{12}H_{19}N_3O$ (M= 221.305)
 Calc.: molpeak (M+H)⁺: 222
 Found: molpeak (M+H)⁺: 222
 R_f value: 0.50 (silica gel, dichloromethane / MeOH / conc. aqueous ammonia
 25 90:10:1).

142c) N-{4-[acetyl-(2-dimethylamino-ethyl)-amino]-phenyl}-2-(2-chloro-4-trifluoromethyl-phenoxy)-acetamide

The product was prepared according to general working method I from (2-chloro-4-trifluoromethyl-phenoxy)-acetic acid (Z2b) and N-(4-amino-phenyl)-N-(2-dimethylamino-ethyl)-acetamide (142b).

Yield: 0.200 g (64% of theory)

5 C₂₁H₂₃ClF₃N₃O₃ (M= 457.884)

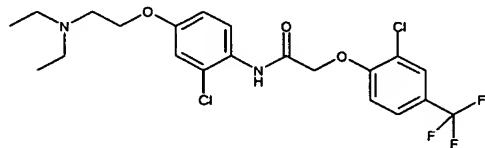
Calc.: molpeak (M+H)⁺: 458/460

Found: molpeak (M+H)⁺: 458/460 (Cl)

R_f value: 0.64 (Alox, dichloromethane / MeOH 19:1).

10

Example 143:



143) N-[2-chloro-4-(2-diethylamino-ethoxy)-phenyl]-2-(2-chloro-4-trifluoromethyl-phenoxy)-acetamide

15 0.141 mL (1.080 mmol) chloroformic acid-isopropylester was added dropwise at -10 °C to a solution of 0.254 g (0.982 mmol) (2-chloro-4-trifluoromethyl-phenoxy)-acetic acid (Z2b) and 0.119 mL (1.080 mmol) N-methylmorpholine in 20 mL abs. THF and the mixture was stirred for a further 10 min.. 0.250 g (1.031 mmol) 2-chloro-4-(2-diethylamino-ethoxy)-phenylamine (Z27b) was added, the mixture was
20 stirred for 1 h at RT and then evaporated down i. vac. Water was added and the aqueous phase was exhaustively extracted with dichloromethane. The combined org. phases were dried over sodium sulphate, evaporated down i. vac. and the residue stirred with ether. The precipitate was filtered off, washed with ether and dried in a HV.

25 Yield: 0.210 g (45% of theory)

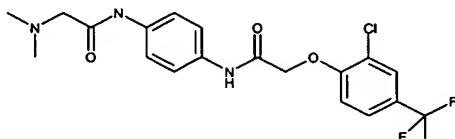
C₂₁H₂₃Cl₂F₃N₂O₃ (M= 479.330)

Calc.: molpeak (M+H)⁺: 479/481/483

Found: molpeak (M+H)⁺: 479/481/483 (Cl₂)

R_f value: 0.67 (Alox, dichloromethane / MeOH 39:1).

Example 144:



5

144) 2-(2-chloro-4-trifluoromethyl-phenoxy)-N-[4-(2-dimethylamino-acetyl)phenyl]-acetamide

Prepared analogously to Example 143 starting from (2-chloro-4-trifluoromethyl-phenoxy)-acetic acid (Z2b) and N-(4-amino-phenyl)-2-dimethylamino-acetamide.

10 Yield: 0.270 g (64% of theory)

$\text{C}_{19}\text{H}_{19}\text{ClF}_3\text{N}_3\text{O}_3$ (M= 429.830)

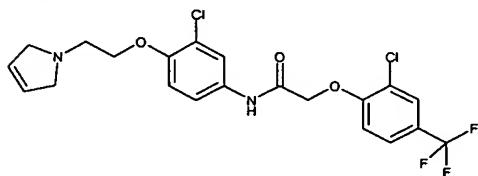
Calc.: molpeak ($\text{M}+\text{H}$)⁺: 430/432

Found: molpeak ($\text{M}+\text{H}$)⁺: 430/432 (Cl)

R_f value: 0.82 (Alox, dichloromethane / MeOH 39:1).

15

Example 145:



145) N-{3-chloro-4-[2-(2,5-dihydro-pyrrol-1-yl)-ethoxy]-phenyl}-2-(2-chloro-4-

20 trifluoromethyl-phenoxy)-acetamide

A solution of 0.145 g (0.300 mmol) of N-[4-(2-bromo-ethoxy)-3-chloro-phenyl]-2-(2-chloro-4-trifluoromethyl-phenoxy)-acetamide (Z28b) and 30.6 μL (0.400 mmol) 2,5-dihydro-1H-pyrrole in 2 mL Hünig base was stirred for 3h at 80 °C and then evaporated down i. vac. Column chromatography (Alox, neutral, act. II-III,

25 gradient dichloromethane / MeOH 20:0 → 19:1) yielded the product.

Yield: 85 mg (60% of theory)

$C_{21}H_{19}Cl_2F_3N_2O_3$ ($M= 475.298$)

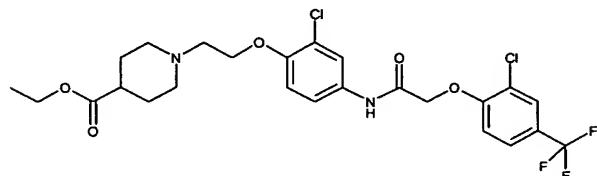
Calc.: molpeak ($M+H$)⁺: 475/477/479

Found: molpeak ($M+H$)⁺: 475/477/479 (Cl_2)

R_f value: 0.35 (Alox, dichloromethane / MeOH 19:1).

5

Example 146:



146) ethyl 1-(2-{2-chloro-4-[2-(2-chloro-4-trifluoromethyl-phenoxy)-acetylamino]-phenoxy}-ethyl)-piperidine-4-carboxylate

Prepared analogously to Example 145 starting from N-[4-(2-bromo-ethoxy)-3-chloro-phenyl]-2-(2-chloro-4-trifluoromethyl-phenoxy)-acetamide (Z28b) and ethyl piperidine-4-carboxylate.

Yield: 190 mg (82% of theory)

15 $C_{25}H_{27}Cl_2F_3N_2O_5$ ($M= 563.406$)

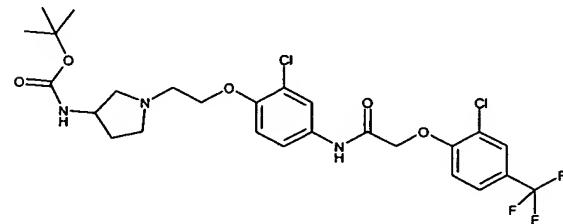
Calc.: molpeak ($M+H$)⁺: 563/565/567

Found: molpeak ($M+H$)⁺: 563/565/567 (Cl_2)

R_f value: 0.52 (silica gel, dichloromethane / MeOH 9:1).

20

Example 147:



147) tert-butyl [1-(2-{2-chloro-4-[2-(2-chloro-4-trifluoromethyl-phenoxy)-acetylamino]-phenoxy}-ethyl)-pyrrolidin-3-yl]-carbaminate

Prepared analogously to Example 145 starting from N-[4-(2-bromo-ethoxy)-3-chloro-phenyl]-2-(2-chloro-4-trifluoromethyl-phenoxy)-acetamide (Z28b) and tert-butyl pyrrolidin-3-yl-carbaminate.

Yield: 230 mg (95% of theory)

5 C₂₆H₃₀Cl₂F₃N₃O₅ (M= 592.447)

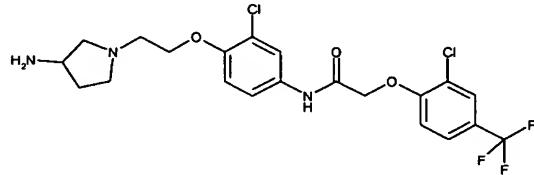
Calc.: molpeak (M+H)⁺: 592/594/596

Found: molpeak (M+H)⁺: 592/594/596 (Cl₂)

R_f value: 0.55 (silica gel, dichloromethane / MeOH 19:1).

10

Example 148:



148) N-[4-{2-(3-amino-pyrrolidin-1-yl)-ethoxy}-3-chloro-phenyl]-2-(2-chloro-4-trifluoromethyl-phenoxy)-acetamide

15 0.80 mL (10.380 mmol) TFA was added at RT to a solution of 0.230 g (0.340 mmol) tert-butyl [1-(2-{2-chloro-4-[2-(2-chloro-4-trifluoromethyl-phenoxy)-acetylamino]-phenoxy}-ethyl)-pyrrolidin-3-yl]-carbaminate (Example 147) in 2 mL dichloromethane and the mixture was stirred for 16 h. The reaction mixture was evaporated down i. vac. and the residue triturated with ether. The precipitate was 20 filtered off, washed with ether and dried in a HV. The product was obtained as the bis-trifluoroacetate salt.

Yield: 230 mg (94% of theory)

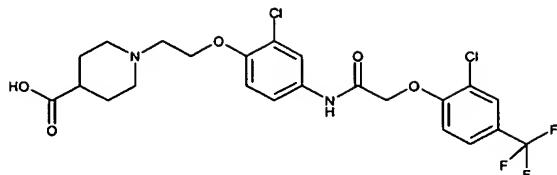
C₂₁H₂₂Cl₂F₃N₃O₃ * 2 C₂HF₃O₂ (M= 720.378)

Calc.: molpeak (M+H)⁺: 492/494/496

25 Found: molpeak (M+H)⁺: 492/494/496 (Cl₂)

R_f value: 0.45 (Alox, dichloromethane / MeOH 19:1).

Example 149:



149) 1-(2-{2-chloro-4-[2-(2-chloro-4-trifluoromethyl-phenoxy)-acetylamino]-phenoxy}-ethyl)-piperidin-4-carboxylic acid

5 2 mL aqueous NaOH (1 M) was added at RT to a solution of 150 mg (0.270 mmol) ethyl 1-(2-{2-chloro-4-[2-(2-chloro-4-trifluoromethyl-phenoxy)-acetylamino]-phenoxy}-ethyl)-piperidine-4-carboxylate (Example 146) in 4 mL EtOH and the mixture was stirred for 16 h. The reaction mixture was neutralised with 2 mL aqueous HCl (1 M), evaporated down i. vac. and the crude product was purified
10 by column chromatography (silica gel, dichloromethane / MeOH 4:1).

Yield: 100 mg (69% of theory)

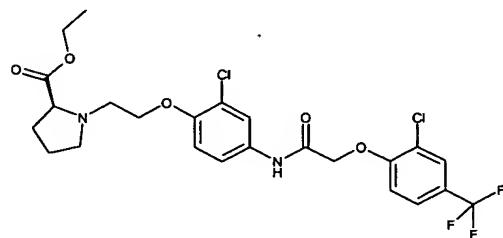
$C_{23}H_{23}Cl_2F_3N_2O_5$ ($M= 535.351$)

Calc.: molpeak $(M+H)^+$: 535/537/539

Found: molpeak $(M+H)^+$: 535/537/539 (Cl_2)

15 R_f value: 0.35 (silica gel, dichloromethane / MeOH 4:1).

Example 150:



20 150) ethyl (S)-1-(2-{2-chloro-4-[2-(2-chloro-4-trifluoromethyl-phenoxy)-acetylamino]-phenoxy}-ethyl)-pyrrolidine-2-carboxylate

Prepared analogously to Example 145 starting from N-[4-(2-bromo-ethoxy)-3-chloro-phenyl]-2-(2-chloro-4-trifluoromethyl-phenoxy)-acetamide (Z28b) and ethyl (S)-pyrrolidine-2-carboxylate .

Yield: 200 mg (89% of theory)

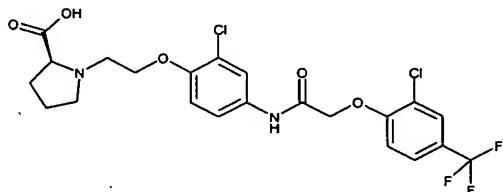


Calc.: molpeak ($M+H$) $^+$: 549/551/553

Found: molpeak ($M+H$) $^+$: 549/551/553 (Cl_2)

5 R_f value: 0.53 (Alox, dichloromethane / MeOH 49:1).

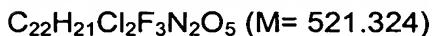
Example 151:



10 151) (S)-1-(2-{2-chloro-4-[2-(2-chloro-4-trifluoromethyl-phenoxy)-acetylamino]-phenoxy}-ethyl)-pyrrolidine-2-carboxylic acid

Prepared analogously to Example 149 starting from ethyl (S)-1-(2-{2-chloro-4-[2-(2-chloro-4-trifluoromethyl-phenoxy)-acetylamino]-phenoxy}-ethyl)-pyrrolidine-2-carboxylate (Example 150).

15 Yield: 114 mg (30% of theory)

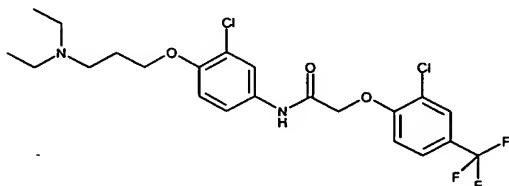


Calc.: molpeak ($M+H$) $^+$: 521/523/525

Found: molpeak ($M+H$) $^+$: 521/523/525 (Cl_2).

20

Example 152:



152) N-[3-chloro-4-(3-diethylamino-propoxy)-phenyl]-2-(2-chloro-4-trifluoromethyl-phenoxy)-acetamide

Prepared analogously to Example 145 starting from N-[4-(2-bromo-ethoxy)-3-chloro-phenyl]-2-(2-chloro-4-trifluoromethyl-phenoxy)-acetamide (Z28b) and 3-chloro-4-(3-diethylamino-propoxy)-phenylamine (Z29b).

Yield: 330 mg (68% of theory)

5 C₂₂H₂₅Cl₂F₃N₂O₃ (M= 493.357)

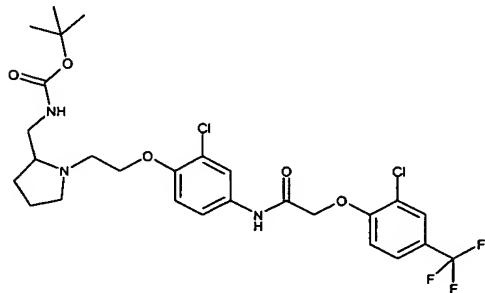
Calc.: molpeak (M+H)⁺: 493/495/497

Found: molpeak (M+H)⁺: 493/495/497 (Cl₂).

R_f value: 0.30 (silica gel, dichloromethane / MeOH / conc. aqueous ammonia 90:10:0.1).

10

Example 153:



153) tert. butyl [1-(2-{2-chloro-4-[2-(2-chloro-4-trifluoromethyl-phenoxy)-

15 acetylaminophenoxy}-ethyl)-pyrrolidin-2-ylmethyl]-carbaminate

Prepared analogously to Example 143 starting from N-[4-(2-bromo-ethoxy)-3-chloro-phenyl]-2-(2-chloro-4-trifluoromethyl-phenoxy)-acetamide (Z28b) and tert-butyl pyrrolidin-2-ylmethyl-carbaminate.

Yield: 280 mg (quant. yield)

20 C₂₇H₃₂Cl₂F₃N₃O₅ (M= 606.474)

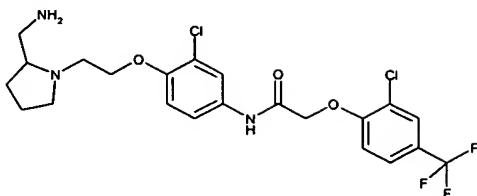
Calc.: molpeak (M-H)⁻: 604/606/608

Found: molpeak (M-H)⁻: 604/606/608 (Cl₂).

R_f value: 0.85 (Alox, dichloromethane / MeOH 19:1).

25

Example 154:



154) N-{4-[2-(2-aminomethyl-pyrrolidin-1-yl)-ethoxy]-3-chloro-phenyl}-2-(2-chloro-4-trifluoromethyl-phenoxy)-acetamide

5 Prepared analogously to Example 148 starting from tert. butyl [1-(2-{2-chloro-4-[2-(2-chloro-4-trifluoromethyl-phenoxy)-acetylamino]-phenoxy}-ethyl)-pyrrolidin-2-ylmethyl]-carbaminate (Example 153).

Yield: 280 mg (quant. yield)

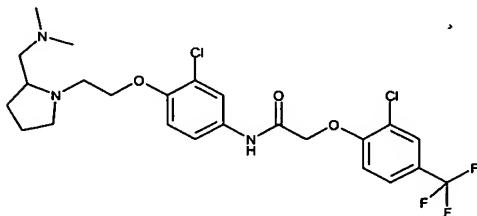
$C_{22}H_{24}Cl_2F_3N_3O_3 * C_2HF_3O_2$ ($M = 734.405$)

10 Calc.: molpeak ($M-H^-$): 504/506/508

Found: molpeak ($M-H^-$): 504/506/508 (Cl_2).

R_f value: 0.14 (Alox, dichloromethane / MeOH 19:1).

15 Example 155:



155) N-{3-chloro-4-[2-(2-dimethylaminomethyl-pyrrolidin-1-yl)-ethoxy]-phenyl}-2-(2-chloro-4-trifluoromethyl-phenoxy)-acetamide

0.46 mL (6.080 mmol) formaldehyde (37% in water) was added to a solution of
20 250 mg (0.340 mmol) N-{4-[2-(2-aminomethyl-pyrrolidin-1-yl)-ethoxy]-3-chloro-phenyl}-2-(2-chloro-4-trifluoromethyl-phenoxy)-acetamide (Example 154) in 7 mL MeOH and the mixture was stirred for 1 h at RT. 103 mg (2.720 mmol) sodium borohydride was added batchwise and the mixture was stirred for a further 16 h at RT. The reaction mixture was evaporated down i. vac. and the residue was taken

up in dichloromethane. The org. phase was washed with saturated aqueous sodium bicarbonate, dried over sodium sulphate and evaporated down i. vac. Column chromatography (silica gel, dichloromethane / MeOH 49:1) yielded the product.

5 Yield: 170 mg (94% of theory)



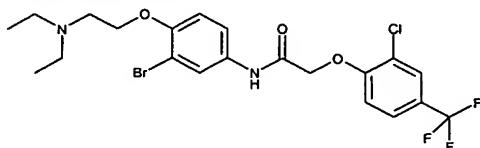
Calc.: molpeak $(\text{M}+\text{H})^+$: 534/536/538

Found: molpeak $(\text{M}+\text{H})^+$: 534/536/538 (Cl_2).

R_f value: 0.58 (Alox, dichloromethane / MeOH 19:1).

10

Example 156:



156) N-[3-bromo-4-(2-diethylaminoethoxy)-phenyl]-2-(2-chloro-4-trifluoromethylphenoxy)-acetamide

Prepared analogously to Example 143 starting from (2-chloro-4-trifluoromethylphenoxy)-acetic acid (Z2b) and 3-bromo-4-(2-diethylaminoethoxy)-phenylamine (Z30b).

Yield: 0.310 g (60% of theory)

20 $\text{C}_{21}\text{H}_{23}\text{BrClF}_3\text{N}_2\text{O}_3 \quad (\text{M} = 523.781)$

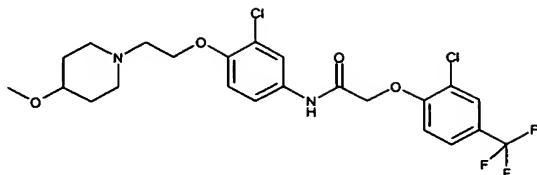
Calc.: molpeak $(\text{M}+\text{H})^+$: 523/525/527

Found: molpeak $(\text{M}+\text{H})^+$: 523/525/527 (BrCl).

R_f value: 0.64 (Alox, dichloromethane / MeOH 39:1).

25

Example 157:



157) N-{3-chloro-4-[2-(4-methoxy-piperidin-1-yl)-ethoxy]-phenyl}-2-(2-chloro-4-trifluoromethyl-phenoxy)-acetamide

5 Prepared analogously to Example 145 starting from N-[4-(2-bromo-ethoxy)-3-chloro-phenyl]-2-(2-chloro-4-trifluoromethyl-phenoxy)-acetamide (Z28b) and 4-methoxy-piperidine.

Yield: 0.200 g (94% of theory)

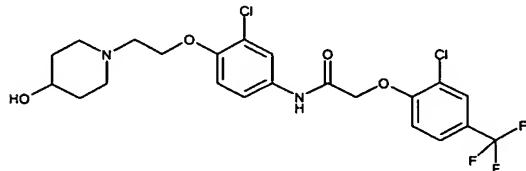
$C_{23}H_{25}Cl_2F_3N_2O_4$ ($M= 521.368$)

10 Calc.: molpeak ($M+H^+$): 521/523/525

Found: molpeak ($M+H^+$): 521/523/525 (Cl_2).

R_f value: 0.75 (Alox, dichloromethane / MeOH 49:1).

15 Example 158:



158) N-{3-chloro-4-[2-(4-hydroxy-piperidin-1-yl)-ethoxy]-phenyl}-2-(2-chloro-4-trifluoromethyl-phenoxy)-acetamide

20 Prepared analogously to Example 145 starting from N-[4-(2-bromo-ethoxy)-3-chloro-phenyl]-2-(2-chloro-4-trifluoromethyl-phenoxy)-acetamide (Z28b) and 4-hydroxy-piperidine.

Yield: 0.190 g (91% of theory)

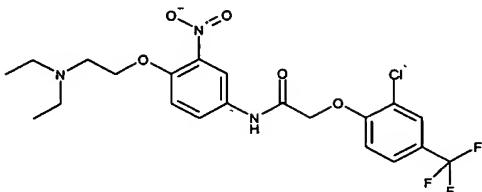
$C_{22}H_{23}Cl_2F_3N_2O_4$ ($M= 507.341$)

Calc.: molpeak ($M+H^+$): 507/509/511

25 Found: molpeak ($M+H^+$): 507/509/511 (Cl_2).

R_f value: 0.55 (Alox, dichloromethane / MeOH 19:1).

Example 159:



5

159) 2-(2-chloro-4-trifluoromethyl-phenoxy)-N-[4-(2-diethylamino-ethoxy)-3-nitro-phenyl]-acetamide

Prepared analogously to Example 143 starting from (2-chloro-4-trifluoromethyl-phenoxy)-acetic acid (Z2b) and 4-(2-diethylamino-ethoxy)-3-nitro-phenylamine

10 (Z31a).

Yield: 0.410 g (45% of theory)

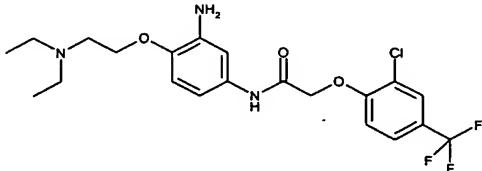
$C_{21}H_{23}ClF_3N_3O_5$ ($M= 489.883$)

Calc.: molpeak $(M+H)^+$: 490/492

Found: molpeak $(M+H)^+$: 490/492 (Cl).

15 R_f value: 0.46 (silica gel, dichloromethane / MeOH 9:1).

Example 160:



20 160) N-[3-amino-4-(2-diethylaminoethoxy)-phenyl]-2-(2-chloro-4-trifluoromethyl-phenoxy)-acetamide

A suspension of 330 mg (0.674 mmol) 2-(2-chloro-4-trifluoromethyl-phenoxy)-N-[4-(2-diethylamino-ethoxy)-3-nitro-phenyl]-acetamide (Example 160) and 200 mg

Raney nickel was hydrogenated at RT and 3 bar. The catalyst was filtered off and the filtrate evaporated down i. vac. .

Yield: 0.310 g (quant. yield)

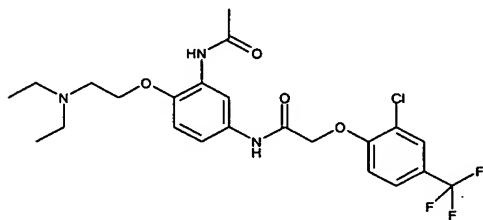
$C_{21}H_{25}ClF_3N_3O_3$ ($M= 459.900$)

5 Calc.: molpeak $(M+H)^+$: 460/462

Found: molpeak $(M+H)^+$: 460/462 (Cl).

R_f value: 0.45 (silica gel, dichloromethane / MeOH 9:1).

10 Example 161:



161) N -[3-acetylaminophenyl]-2-(2-chloro-4-trifluoromethylphenoxy)-acetamide

A solution of 100 mg (0.217 mmol) N -[3-amino-4-(2-diethylaminoethoxy)-phenyl]-2-(2-chloro-4-trifluoromethyl-phenoxy)-acetamide (Example 160) in 10 mL acetic anhydride was stirred for 3 h at 100 °C and then evaporated down i. vac. . The residue was combined with saturated aqueous sodium bicarbonate and exhaustively extracted with EtOAc. The combined org. phases were dried over sodium sulphate, evaporated down i. vac. and the residue was stirred with ether.

20 The precipitate was filtered off, washed with ether and dried in a HV.

Yield: 0.108 g (quant. yield)

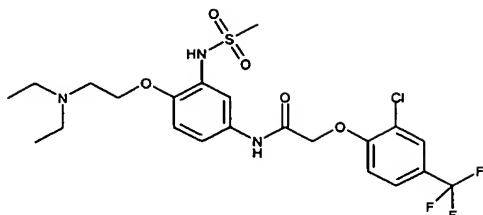
$C_{23}H_{27}ClF_3N_3O_4$ ($M= 501.938$)

Calc.: molpeak $(M+H)^+$: 502/504

Found: molpeak $(M+H)^+$: 502/504 (Cl).

25 R_f value: 0.42 (silica gel, dichloromethane / MeOH 9:1).

Example 162:



162) 2-(2-chloro-4-trifluoromethyl-phenoxy)-N-[4-(2-diethylamino-ethoxy)-3-methanesulphonylamino-phenyl]-acetamide

5 A solution of 100 mg (0.217 mmol) N-[3-amino-4-(2-diethylamino-ethoxy)-phenyl]-2-(2-chloro-4-trifluoromethyl-phenoxy)-acetamide (Example 160) in 5 mL pyridine was added at 0 °C to 18 µL (0.239 mmol) of methanesulphonylchloride, the mixture was slowly heated to RT and stirred for 3 h at RT. The reaction mixture was poured onto ice water and the aqueous phase was exhaustively extracted
10 with EtOAc. The combined org. phases were dried over sodium sulphate and evaporated down i. vac. . The residue was lyophilised.

Yield: 0.080 g (87% of theory)

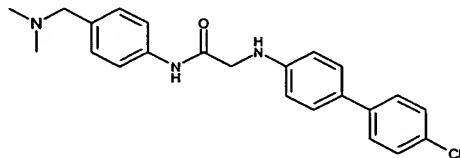
$C_{22}H_{27}ClF_3N_3O_5S$ ($M= 537.990$)

Calc.: molpeak ($M+H$) $^+$: 538/540

15 Found: molpeak ($M+H$) $^+$: 538/540 (Cl).

R_f value: 0.40 (silica gel, dichloromethane / MeOH 9:1).

Example 163:



20

163a) 2-(4-bromo-phenylamino)-N-(4-dimethylaminomethyl-phenyl)-acetamide

The product was prepared according to general working method I from (4-bromo-phenylamino)-acetic acid and 4-dimethylaminomethyl-phenylamine.

Yield: 1.340 g (28% of theory)

$C_{17}H_{20}BrN_3O$ ($M= 362.272$)

Calc.: molpeak ($M+H$) $^+$: 362/364

Found: molpeak ($M+H$) $^+$: 362/364 (Cl).

R_f value: 0.68 (Alox, dichloromethane / MeOH 19:1).

5

163b) 2-(4'-chloro-biphenyl-4-ylamino)-N-(4-dimethylaminomethyl-phenyl)-acetamide

Prepared analogously to Example 130a starting from 2-(4-bromo-phenylamino)-N-(4-dimethylaminomethyl-phenyl)-acetamide (Example 163a) and 4-chloro-phenyl-

10 boric acid.

Yield: 0.160 g (41% of theory)

$C_{23}H_{24}ClN_3O$ ($M= 393.920$)

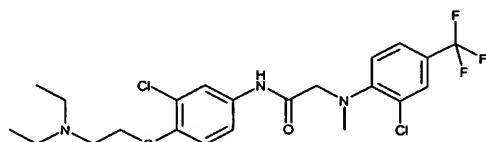
Calc.: molpeak ($M+H$) $^+$: 394/396

Found: molpeak ($M+H$) $^+$: 394/396 (Cl).

15 R_f value: 0.48 (silica gel, dichloromethane / MeOH / conc. aqueous ammonia 90:10:1).

Example 164:

20



164a) (2-chloro-4-trifluoromethyl-phenyl)-methyl-amine

7.04 mL (59.059 mmol) N,N-dimethyl-formamide-dimethylacetal was added to a

solution of 2.100 g (10.738 mmol) 2-chloro-4-trifluoromethoxy-phenylamine in 10

mL DMF under a nitrogen atmosphere and the mixture was stirred for 5 h at 60 °C

25 and for 16 h at RT. 1.421 g (37.583 mmol) sodium borohydride was added and the mixture was stirred for another 3 h at 60 °C. Saturated aqueous sodium

bicarbonate was added and the mixture was extracted with EtOAc. The org.

phase was dried over sodium sulphate and evaporated down i. vac. at 30 °C.

Column chromatography (silica gel, petroleum ether) yielded the product.

Yield: 1.100 g (49% of theory)

$C_8H_7ClF_3N$ ($M= 209.600$)

Calc.: molpeak ($M+H$) $^+$: 210/212

Found: molpeak ($M+H$) $^+$: 210/212 (Cl).

5 R_f value: 0.75 (silica gel, petroleum ether / EtOAc 9:1).

164b) N -[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-2-[(2-chloro-4-trifluoromethyl-phenyl)-methyl-amino]-acetamide

A solution of 0.200 g (0.450 mmol) 2-bromo- N -[3-chloro-4-(2-diethylamino-

10 ethoxy)-phenyl]-acetamide-hydrobromide and 0.141 g (0.675 mmol) (2-chloro-4-trifluoromethyl-phenyl)-methyl-amine (Example 164a) in 2 mL DMF was heated to 100 °C for 2 h in the microwave. The reaction mixture was evaporated down i. vac., diluted with 3 mL DMF and purified by HPLC-MS (Stable Bond C18; 3.5 μ m; water:acetonitrile:formic acid 9:1:0.01 → 1:9:0.01 over 9 min). The product was obtained as the formate salt.

15 Yield: 36 mg (15% of theory)

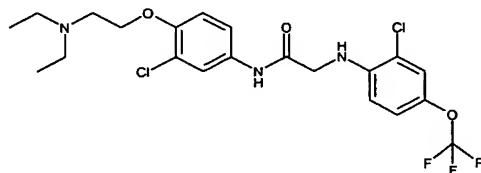
$C_{22}H_{26}Cl_2F_3N_3O_2 * CH_2O_2$ ($M= 538.399$)

Calc.: molpeak ($M+H$) $^+$: 492/494/496

Found: molpeak ($M+H$) $^+$: 492/494/496 (Cl₂).

20 R_f value: 0.69 (silica gel, EtOAc / MeOH / conc. aqueous ammonia 90:10:1).

Example 165:

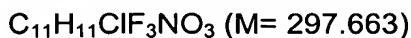


25 165a) ethyl (2-chloro-4-trifluoromethoxy-phenyl-amino)-acetate

0.566 mL (5.000 mmol) ethyl bromoacetate was added at RT to a solution of 0.95 g (4.266 mmol) (2-chloro-4-trifluoromethyl-phenyl)-methyl-amine in 10 mL Hünig base and the mixture was refluxed for 4 h. Water was added and the aqueous

phase was exhaustively extracted with EtOAc. The combined org. phases were washed with water, saturated aqueous sodium bicarbonate and saturated aqueous NaCl, dried over sodium sulphate and evaporated down i. vac. . The crude product was used in the next reaction step without any further purification.

5 Yield: 1.200 g (57% of theory)

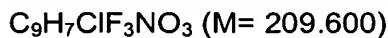


R_f value: 0.68 (silica gel, petroleum ether / EtOAc 3:1).

165b) (2-chloro-4-trifluoromethoxy-phenyl-amino)-acetic acid

10 Prepared analogously to Intermediate product Z2b starting from ethyl [(2-chloro-4-trifluoromethyl-phenyl)-methyl-amino]-acetate (Example 165a).

Yield: 0.630 g (97% of theory)



Calc.: molpeak (M+H)⁺: 210/212

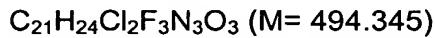
15 Found: molpeak (M+H)⁺: 210/212 (Cl).

R_f value: 0.75 (silica gel, petroleum ether / EtOAc 9:1).

165c) N-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-2-(2-chloro-4-trifluoromethoxy-phenylamino)-acetamide

20 The product was prepared according to general working method I from (2-chloro-4-trifluoromethoxy-phenyl-amino)-acetic acid (Example 165b) and 3-chloro-4-(2-diethylamino-ethoxy)-phenylamine (Z1b).

Yield: 0.220 g (44% of theory)

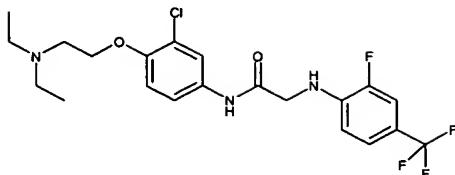


25 Calc.: molpeak (M-H)⁻: 492/494/496

Found: molpeak (M-H)⁻: 492/494/496 (Cl).

R_f value: 0.48 (Alox, dichloromethane / MeOH 30:1).

Example 166:



166a) ethyl (2-fluoro-4-trifluoromethyl-phenylamino)-acetate

Prepared analogously to Example 165a starting from 2-fluoro-4-trifluoromethyl-phenylamine and ethyl bromoacetate. The crude product was purified by column chromatography (silica gel, gradient dichloromethane / MeOH 20:0 → 19:1).

Yield: 0.980 g (82% of theory)

$C_{11}H_{11}F_4NO_2$ ($M= 265.209$)

Calc.: molpeak $(M+H)^+$: 266

10 Found: molpeak $(M+H)^+$: 266

R_f value: 0.72 (silica gel, petroleum ether / EtOAc 3:1).

166b) (2-fluoro-4-trifluoromethyl-phenylamino)-acetic acid

15 Prepared analogously to Intermediate product Z2b starting from ethyl (2-fluoro-4-trifluoromethyl-phenylamino)-acetate (Example 166a). The crude product was purified by column chromatography (silica gel, gradient dichloromethane / MeOH 20:0 → 19:1).

Yield: 0.670 g (79% of theory)

$C_9H_7F_4NO_2$ ($M= 237.155$)

20 Calc.: molpeak $(M-H)^-$: 236

Found: molpeak $(M-H)^-$: 236.

166c) N-[3-chloro-4-(2-diethylaminoethoxy)-phenyl]-2-(2-fluoro-4-trifluoromethyl-phenylamino)-acetamide

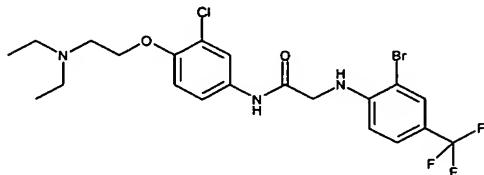
25 The product was obtained according to general working method I starting from (2-fluoro-4-trifluoromethyl-phenylamino)-acetic acid (Example 166b) and 3-chloro-4-(2-diethylaminoethoxy)-phenylamine (Z1b).

Yield: 0.150 g (32% of theory)

$C_{21}H_{24}ClF_4N_3O_2$ ($M= 461.891$)
 Calc.: molpeak ($M+H$) $^+$: 462/464
 Found: molpeak ($M+H$) $^+$: 462/464 (Cl)

5

Example 167:



167a) ethyl (2-bromo-4-trifluoromethyl-phenylamino)-acetate

Prepared analogously to Example 166a starting from 2-bromo-4-trifluoromethyl-
 10 phenylamine and ethyl bromoacetate.

Yield: 1.200 g (36% of theory)

$C_{11}H_{11}BrF_3NO_2$ ($M= 326.115$)

R_f value: 0.72 (silica gel, petroleum ether / EtOAc 3:1).

15 167b) (2-bromo-4-trifluoromethyl-phenylamino)-acetic acid

Prepared analogously to Intermediate product Z2b starting from ethyl (2-bromo-4-trifluoromethyl-phenylamino)-acetate (Example 167a).

Yield: 0.438 g (quant. yield)

$C_9H_7BrF_3NO_2$ ($M= 298.061$)

20 Calc.: molpeak ($M-H$) $^-$: 296/298

Found: molpeak ($M-H$) $^-$: 296/298.

167c) 2-(2-bromo-4-trifluoromethyl-phenylamino)-N-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-acetamide

25 The product was obtained according to general working method I starting from (2-bromo-4-trifluoromethyl-phenylamino)-acetic acid (Example 167b) and 3-chloro-4-(2-diethylamino-ethoxy)-phenylamine (Z1b).

Yield: 0.300 g (84% of theory)

$C_{21}H_{24}BrClF_3N_3O_2$ ($M= 522.797$)

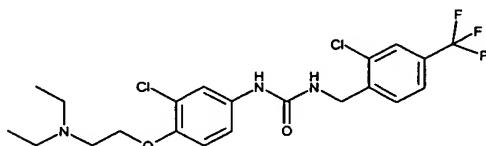
Calc.: molpeak ($M+H$) $^+$: 522/524/526

Found: molpeak ($M+H$) $^+$: 522/524/526 (BrCl)

R_f value: 0.45 (silica gel, dichloromethane / MeOH 9:1).

5

Example 168:



168a) 2-chloro-4-trifluoromethyl-benzylamine

10 A suspension of 1.000 g (4.865 mmol) 2-chloro-4-trifluoromethyl-benzonitrile and 100 mg Raney nickel in conc. methanolic ammonia was hydrogenated for 20 h at RT and 3 bar. The catalyst was filtered off and the filtrate was evaporated down i. vac. .

Yield: 0.870 g (85% of theory)

15 $C_8H_7ClF_3N$ ($M= 209.600$)

Calc.: molpeak ($M+H$) $^+$: 210/212

Found: molpeak ($M+H$) $^+$: 210/212 (Cl)

R_f value: 0.48 (silica gel, petroleum ether / EtOAc 2:1).

20 168b) 1-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-3-(2-chloro-4-trifluoromethyl-benzyl)-urea

0.770 g (4.457 mmol) CDT was added at 0 °C to a solution of 0.870 g (4.151 mmol) 2-chloro-4-trifluoromethyl-benzylamine (Example 168a) in 50 mL abs. THF and the mixture was stirred for 1 h at RT. 1.080 g (4.449 mmol) 3-chloro-4-(2-

25 diethylamino-ethoxy)-phenylamine (Z1b) was added and the mixture was refluxed for 5 h. The reaction mixture was evaporated down i. vac. and the residue was taken up in dichloromethane. The org. phase was washed with 15% aqueous potassium carbonate, dried over sodium sulphate and evaporated down i. vac. .

The crude product was triturated with diisopropylether, the precipitate was filtered off, washed with diisopropylether and dried in a HV.

Yield: 0.570 g (29% of theory)

$C_{21}H_{24}Cl_2F_3N_3O_2$ ($M= 478.346$)

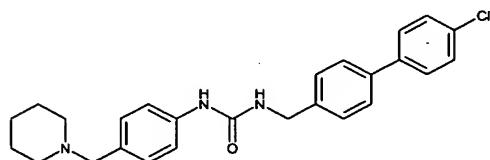
5 Calc.: molpeak ($M+H$)⁺: 478/480/482

Found: molpeak ($M+H$)⁺: 478/480/482 (Cl_2)

R_f value: 0.36 (silica gel, dichloromethane / MeOH / cyclohexane / conc. aqueous ammonia 70:15:15:2).

10

Example 169:



169) 1-(4'-chloro-biphenyl-4-ylmethyl)-3-(4-piperidin-1-ylmethyl-phenyl)-urea

Prepared analogously to Example 168b starting from C-(4'-chloro-biphenyl-4-yl)-methylamine and 4-piperidin-1-ylmethyl-phenylamine. The crude product was purified by column chromatography (Alox, neutral, act. II-III, dichloromethane / MeOH 98:2).

Yield: 0.390 g (90% of theory)

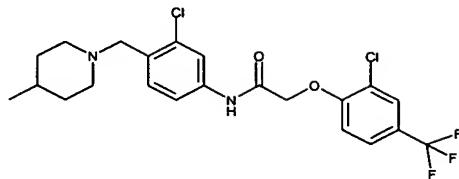
$C_{26}H_{28}ClN_3O$ ($M= 433.986$)

20 Calc.: molpeak ($M+H$)⁺: 434/436

Found: molpeak ($M+H$)⁺: 434/436 (Cl)

R_f value: 0.42 (Alox, dichloromethane / MeOH 39:1).

Example 170:



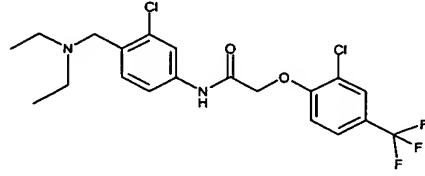
170) N-[3-chloro-4-(4-methyl-piperidin-1-ylmethyl)-phenyl]-2-(2-chloro-4-trifluoromethyl-phenoxy)-acetamide

5 0.24 mL (2.000 mmol) 4-methylpiperidine was added to a solution of 0.206 g (0.500 mmol) N-(3-chloro-4-chloromethyl-phenyl)-2-(2-chloro-4-trifluoromethyl-phenoxy)-acetamide (Z32b) in 5 mL abs. THF and the mixture was refluxed for 2 h. The reaction mixture was poured onto ice water, the precipitate was filtered off, washed with water and dried in a HV.

10 Yield: 0.214 g (90% of theory)
 $C_{22}H_{23}Cl_2F_3N_2O_2$ (M= 475.342)
 Calc.: molpeak $(M+H)^+$: 475/477/479
 Found: molpeak $(M+H)^+$: 475/477/479 (Cl_2)
 R_f value: 0.66 (Alox, petroleum ether / EtOAc 3:1).

15

Example 171:



171) N-(3-chloro-4-diethylaminomethyl-phenyl)-2-(2-chloro-4-trifluoromethyl-phenoxy)-acetamide

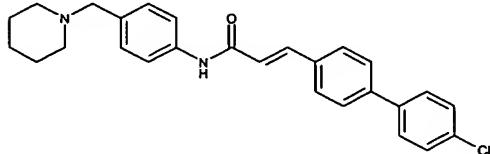
20 Prepared analogously to Example 170 starting from N-(3-chloro-4-chloromethyl-phenyl)-2-(2-chloro-4-trifluoromethyl-phenoxy)-acetamide (Z32b) and diethylamine. The crude product was recrystallised from petroleum ether.
 Yield: 0.154 g (69% of theory)

25 $C_{20}H_{21}Cl_2F_3N_2O_2$ (M= 449.304)

Calc.: molpeak (M+H)⁺: 449/451/453
 Found: molpeak (M+H)⁺: 449/451/453 (Cl₂)
 R_f value: 0.53 (Alox, petroleum ether / EtOAc 3:1).

5

Example 172:



172) (E)-3-(4'-chlorobiphenyl-4-yl)-N-(4-piperidin-1-ylmethyl-phenyl)-acrylamide

A solution of 0.544 g (2.103 mmol) (E)-3-(4'-chlorobiphenyl-4-yl)-acrylic acid,

10 0.440 g (2.313 mmol) 4-piperidin-1-ylmethyl-phenylamine, 0.736 g (2.313 mmol) TBTU, 0.313 g (2.313 mmol) HOBr and 1.025 mL (7.361 mmol) triethylamine in 10 mL DMF was stirred for 3 h at RT and then poured onto ice water and a little EtOAc. The precipitate was filtered off, washed with water and dried at 80 °C i. vac..

15 Yield: 0.154 g (69% of theory)

C₂₇H₂₇ClN₂O (M= 430.982)

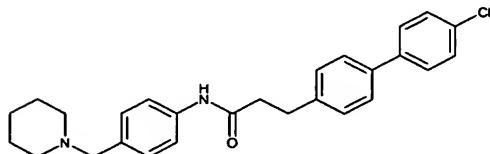
Calc.: molpeak (M+H)⁺: 431/433

Found: molpeak (M+H)⁺: 431/433 (Cl)

R_f value: 0.31 (silica gel, dichloromethane / MeOH 9:1).

20

Example 173:



173) 3-(4'-chlorobiphenyl-4-yl)-N-(4-piperidin-1-ylmethyl-phenyl)-propionamide

25 A suspension of 0.200 g (0.464 mmol) (E)-3-(4'-chlorobiphenyl-4-yl)-N-(4-piperidin-1-ylmethyl-phenyl)-acrylamide (Example 172) and 100 mg Raney nickel

in 50 mL EtOAc was hydrogenated at RT and 50 psi. The catalyst was filtered off, the filtrate was evaporated down i. vac. and the residue was triturated with ether. The precipitate was filtered off, washed with ether and dried at 50 °C i. vac..

Yield: 55 mg (27% of theory)

5 C₂₇H₂₉CIN₂O (M= 432.998)

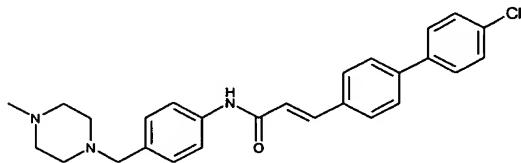
Calc.: molpeak (M+H)⁺: 433/435

Found: molpeak (M+H)⁺: 433/435 (Cl)

R_f value: 0.23 (silica gel, dichloromethane / MeOH 9:1).

10

Example 174:



174) (E)-3-(4'-chloro-biphenyl-4-yl)-N-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-acrylamide

15 Prepared analogously to Example 172 starting from (E)-3-(4'-chloro-biphenyl-4-yl)-acrylic acid and 4-(4-methyl-piperazin-1-ylmethyl)-phenylamine. The crude product was purified by column chromatography (silica gel, dichloromethane / MeOH / conc. aqueous ammonia 90:10:0.1).

Yield: 0.410 g (61% of theory)

20 C₂₇H₂₈CIN₃O (M= 445.997)

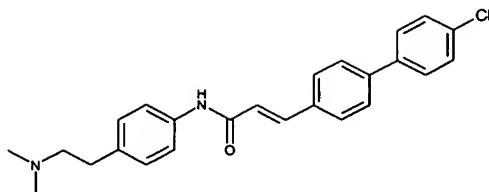
Calc.: molpeak (M+H)⁺: 446/448

Found: molpeak (M+H)⁺: 446/448 (Cl)

R_f value: 0.40 (silica gel, dichloromethane / MeOH 9:1).

25

Example 175:



175) (E)-3-(4'-chloro-biphenyl-4-yl)-N-[4-(2-dimethylamino-ethyl)-phenyl]-acrylamide

5 Prepared analogously to Example 172 starting from (E)-3-(4'-chloro-biphenyl-4-yl)-acrylic acid and 4-(2-dimethylamino-ethyl)-phenylamine.

Yield: 0.350 g (58% of theory)

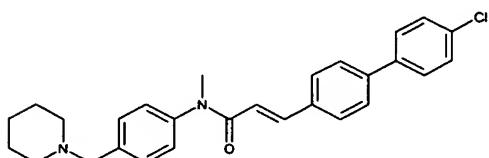
$C_{25}H_{25}ClN_2O$ ($M= 404.944$)

Calc.: molpeak ($M+H$) $^+$: 405/407

10 Found: molpeak ($M+H$) $^+$: 405/407 (Cl)

R_f value: 0.40 (silica gel, dichloromethane / MeOH / conc. aqueous ammonia 90:10:0.1).

15 Example 176:



176) (E)-3-(4'-chloro-biphenyl-4-yl)-N-methyl-N-(4-piperidin-1-ylmethyl-phenyl)-acrylamide

Prepared analogously to Example 172 starting from (E)-3-(4'-chloro-biphenyl-4-yl)-acrylic acid and methyl-(4-piperidin-1-ylmethyl-phenyl)-amine.

Yield: 0.200 g (45% of theory)

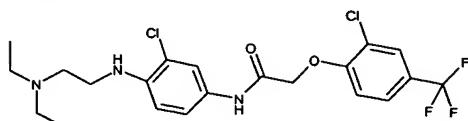
$C_{28}H_{29}ClN_2O$ ($M= 445.009$)

Calc.: molpeak ($M+H$) $^+$: 445/447

Found: molpeak ($M+H$) $^+$: 445/447 (Cl)

R_f value: 0.60 (silica gel, dichloromethane / MeOH / conc. aqueous ammonia 90:10:0.1).

5 Example 177:



177) N-[3-chloro-4-(2-diethylamino-ethylamino)-phenyl]-2-(2-chloro-4-trifluoromethyl-phenoxy)-acetamide

The product was prepared according to general working method I starting from
 10 0.270 g (1.060 mmol) (2-chloro-4-trifluoromethyl-phenoxy)-acetic acid (Z2b) and
 0.260 g (1.080 mmol) 2-chloro-*N'*-(2-diethylamino-ethyl)-benzene-1,4-diamine
 (Z42b).

Yield: 0.340 g (67% of theory)

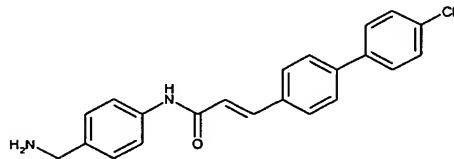
$C_{21}H_{24}Cl_2N_3O_2$ ($M = 478.346$)

15 Calc.: molpeak ($M+H$)⁺: 478/480/482

Found: molpeak ($M+H$)⁺: 478/480/482 (Cl_2)

R_f value: 0.45 (Alox, dichloromethane / MeOH 45:1).

20 Example 178:



178a) tert-butyl {4-[(E)-3-(4'-chlorobiphenyl-4-yl)-acryloylamino]benzyl}carbaminate

Prepared analogously to Example 172 starting from (E)-3-(4'-chloro-biphenyl-4-yl)-acrylic acid and tert-butyl (4-amino-benzyl)-carbaminate. The crude product was stirred with MeOH, the precipitate was filtered off and dried in a HV.

Yield: 1.000 g (72% of theory)

5 $C_{27}H_{27}ClN_2O_3$ ($M= 462.981$)

Calc.: molpeak ($M+H$)⁺: 463/465

Found: molpeak ($M+H$)⁺: 463/465 (Cl)

R_f value: 0.70 (silica gel, dichloromethane / MeOH 9:1).

10

178b) (E)-N-(4-aminomethyl-phenyl)-3-(4'-chloro-biphenyl-4-yl)-acrylamide

5 mL TFA was added at RT to a suspension of 0.950 g (2.050 mmol) tert-butyl {4-[(E) -3-(4'-chloro-biphenyl-4-yl)-acryloylamino]-benzyl}-carbaminate in 50 mL abs. dichloromethane and the mixture was stirred for 2 h at RT . The reaction mixture

15 was evaporated down i. vac. , combined with toluene and again evaporated down i. vac. ..The residue was triturated with ether, the precipitate was filtered off and dried i. vac. at 80 °C . The product was obtained as the trifluoroacetate salt.

Yield: 0.930 g (95% of theory)

$C_{22}H_{19}ClN_2O * C_2HF_3O_2$ ($M= 476.887$)

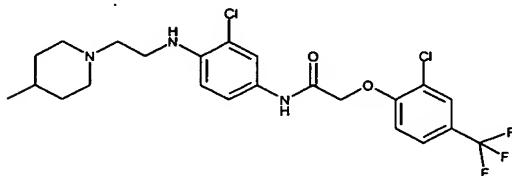
20 Calc.: molpeak ($M+H$)⁺: 363/365

Found: molpeak ($M+H$)⁺: 363/365 (Cl)

R_f value: 0.40 (silica gel, dichloromethane / MeOH / conc. aqueous ammonia 90:10:0.1).

25

Example 179:



179) N-{3-chloro-4-[2-(4-methyl-piperidin-1-yl)-ethylamino]-phenyl}-2-(2-chloro-4-trifluoro-methyl-phenoxy)-acetamide

The product was prepared according to general working method I starting from 0.270 g (1.060 mmol) (2-chloro-4-trifluoromethyl-phenoxy)-acetic acid (Z2b) and 0.290 g (1.080 mmol) 2-chloro-N'-[2-(4-methyl-piperidin-1-yl)-ethyl]-benzene-1,4-diamine (Z43d).

Yield: 0.360 g (67% of theory)

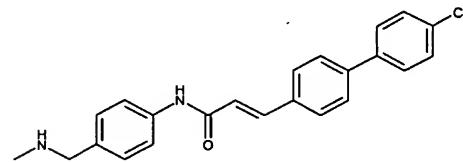
$C_{23}H_{26}Cl_2F_3N_3O_2$ ($M= 503.384$)

Calc.: molpeak ($M+H$)⁺: 504/506/508

10 Found: molpeak ($M+H$)⁺: 504/506/508 (Cl_2)

R_f value: 0.44 (Alox, dichloromethane / MeOH 49:1).

Example 180:



15 180a) tert-butyl {4-[{(E)-3-(4'-chlorobiphenyl-4-yl)-acryloylamino]-benzyl}-methylcarbaminate

Prepared analogously to Example 172 starting from (E)-3-(4'-chlorobiphenyl-4-yl)-acrylic acid and tert-butyl (4-amino-benzyl)-methyl-carbaminate (Z33b). The crude product was stirred with MeOH, the precipitate was filtered off and dried in a HV.

20 Yield: 0.620 g (43% of theory)

$C_{28}H_{29}ClN_2O_3$ ($M= 477.008$)

Calc.: molpeak ($M+H$)⁺: 477/479

Found: molpeak ($M+H$)⁺: 477/479 (Cl)

25 R_f value: 0.80 (silica gel, dichloromethane / MeOH 9:1).

180b) (E)-3-(4'-chlorobiphenyl-4-yl)-N-(4-methylaminomethyl-phenyl)-acrylamide

Prepared analogously to Example 178 starting from tert-butyl {4-[*(E*)-3-(4'-chlorobiphenyl-4-yl)-acryloylamino]-benzyl}-methyl-carbaminate (Example 179). The product was obtained as the trifluoroacetate salt.

Yield: 0.540 g (87% of theory)

5 C₂₃H₂₁CIN₂O * C₂HF₃O₂ (M= 490.914)

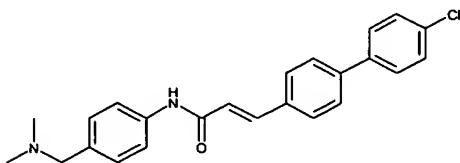
Calc.: molpeak (M+H)⁺: 377/379

Found: molpeak (M+H)⁺: 377/379 (Cl)

R_f value: 0.40 (silica gel, dichloromethane / MeOH / conc. aqueous ammonia 90:10:0.1).

10

Example 181:



181) (E)-3-(4'-chloro-biphenyl-4-yl)-N-(4-dimethylaminomethyl-phenyl)-acrylamide

15 1.00 mL formaldehyde (37% in water) was added at 0 °C to a solution of 0.100 g
(0.280 mmol) (E)-3-(4'-chloro-biphenyl-4-yl)-N-(4-methylaminomethyl-phenyl)-
acrylamide (Example 180) in 1 mL formic acid and the mixture was stirred for 1 h at
RT and 2 h at 90 °C. The reaction mixture was poured onto ice water and the
aqueous phase was exhaustively extracted with EtOAc. The combined org.
20 phases were dried over sodium sulphate, evaporated down i. vac. and the residue
stirred with ether. The precipitate was filtered off, washed with ether and dried i.
vac. at 100 °C.

Yield: 81 mg (74% of theory)

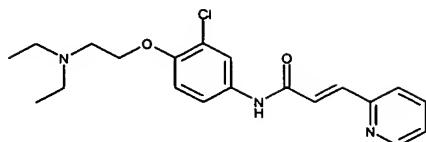
$C_{24}H_{23}ClN_2O$ ($M_r = 390.917$)

25 Calc.: molpeak (M+H)⁺: 391/393

Found: molpeak (M+H)⁺: 391/393 (Cl)

R_f value: 0.50 (silica gel, dichloromethane / MeOH / conc. aqueous ammonia 90:10:0.1).

Example 182:

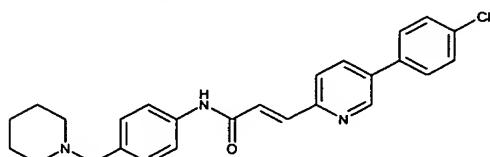


5 182) (E)-N-[3-chloro-4-(2-diethylaminoethoxy)-phenyl]-3-pyridin-2-yl-acrylamide
Prepared analogously to Example 172 starting from (E)-3-pyridin-2-yl-acrylic acid
and 3-chloro-4-(2-diethylaminoethoxy)-phenylamine (Z2b) at RT (72 h). The crude
product was purified by column chromatography (silica gel, dichloromethane /
MeOH / conc. aqueous ammonia 90:10:0.1) and recrystallisation from petroleum
ether.

10 Yield: 0.930 g (50% of theory)
 $C_{20}H_{24}ClN_3O_2$ ($M = 373.886$)
Calc.: molpeak ($M+H^+$): 374/376
Found: molpeak ($M+H^+$): 374/376 (Cl)

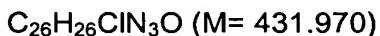
15 R_f value: 0.40 (silica gel, dichloromethane / MeOH / conc. aqueous ammonia
90:10:0.1).

Example 183:



20 183) (E)-3-[5-(4-chlorophenyl)-pyridin-2-yl]-N-(4-piperidin-1-ylmethyl-phenyl)-
acrylamide
Prepared analogously to Example 143 starting from (E)-3-[5-(4-chlorophenyl)-
pyridin-2-yl]-acrylic acid (Z34b) and 4-piperidin-1-ylmethyl-phenylamine. The crude
product was purified by column chromatography (silica gel, dichloromethane /
EtOH / conc. aqueous ammonia 50:10:0.1).

Yield: 0.450 g (52% of theory)

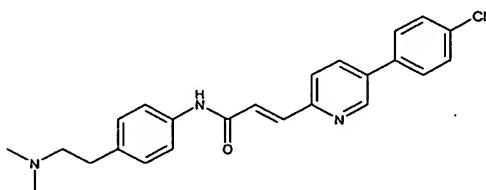


Calc.: molpeak ($M+H$) $^+$: 432/434

Found: molpeak ($M+H$) $^+$: 432/434 (Cl)

5 R_f value: 0.50 (silica gel, dichloromethane / MeOH / conc. aqueous ammonia 90:10:0.1).

Example 184:

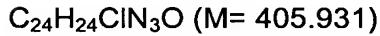


10 184) (E)-3-[5-(4-chloro-phenyl)-pyridin-2-yl]-N-[4-(2-dimethylamino-ethyl)-phenyl]-acrylamide

Prepared analogously to Example 143 starting from (E)-3-[5-(4-chloro-phenyl)-pyridin-2-yl]-acrylic acid (Z34b) and 4-(2-dimethylamino-ethyl)-phenylamine. The crude product was purified by column chromatography (silica gel, dichloromethane

15 / EtOH / conc. aqueous ammonia 50:10:0.1).

Yield: 0.140 g (45% of theory)

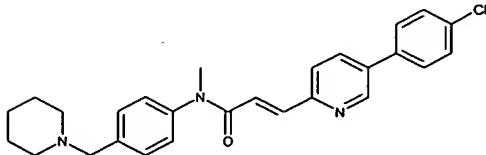


Calc.: molpeak ($M+H$) $^+$: 406/408

Found: molpeak ($M+H$) $^+$: 406/408 (Cl)

20 R_f value: 0.60 (silica gel, dichloromethane / MeOH / conc. aqueous ammonia 90:10:0.1).

Example 185:



185) (E)-3-[5-(4-chloro-phenyl)-pyridin-2-yl]-N-methyl-N-(4-piperidin-1-ylmethyl-phenyl)-acrylamide

Prepared analogously to Example 143 starting from (E)-3-[5-(4-chloro-phenyl)-pyridin-2-yl]-acrylic acid (Z34b) and methyl-(4-piperidin-1-ylmethyl-phenyl)-amine.

5 The crude product was purified by column chromatography (silica gel, dichloromethane / EtOH / conc. aqueous ammonia 50:10:0.1).

Yield: 0.300 g (67% of theory)

$C_{27}H_{28}ClN_3O$ ($M= 445.997$)

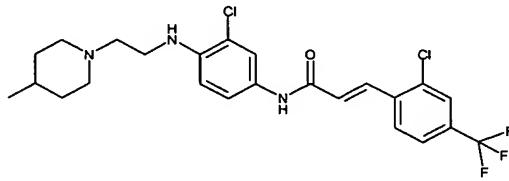
Calc.: molpeak ($M+H$) $^+$: 446/448

10 Found: molpeak ($M+H$) $^+$: 446/448 (Cl)

R_f value: 0.70 (silica gel, dichloromethane / MeOH / conc. aqueous ammonia 90:10:0.1).

Example 186:

15



186) (E)-N-{3-chloro-4-[2-(4-methyl-piperidin-1-yl)-ethylamino]-phenyl}-3-(2-chloro-4-trifluoromethyl-phenyl)-acrylamide

The product was prepared according to general working method I starting from

20 0.250 g (1.000 mmol) (E)-3-(2-chloro-4-trifluoromethyl-phenyl)-acrylic acid (Z37b) and 0.270 g (1.000 mmol) 2-chloro-N'-[2-(4-methyl-piperidin-1-yl)-ethyl]-benzene-1,4-diamine (Z43d) and purified by column chromatography (Alox, neutral, act. II-III gradient dichloromethane / MeOH 100:0 → 49:1).

Yield: 0.220 g (44% of theory)

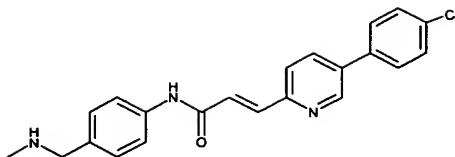
25 $C_{24}H_{26}Cl_2F_3N_3O$ ($M= 500.396$)

Calc.: molpeak ($M+H$) $^+$: 500/502/504

Found: molpeak ($M+H$) $^+$: 500/502/504 (Cl₂)

R_f value: 0.70 (Alox, dichloromethane / MeOH 49:1).

Example 187:



5 187a) tert-butyl (4-{(E)-3-[5-(4-chloro-phenyl)-pyridin-2-yl]-acryloylamino}-benzyl)-methyl-carbaminate

Prepared analogously to Example 182 starting from (E)-3-[5-(4-chloro-phenyl)-pyridin-2-yl]-acrylic acid (Z34b) and tert-butyl (4-amino-benzyl)-carbaminate. The crude product was stirred with MeOH, the precipitate was filtered off and dried in a

10 HV.

Yield: 0.620 g (86% of theory)

$C_{27}H_{28}ClN_3O_3$ ($M = 477.996$)

Calc.: molpeak ($M+H$) $^+$: 478/480

Found: molpeak ($M+H$) $^+$: 478/480 (Cl)

15 R_f value: 0.60 (silica gel, dichloromethane / MeOH 9:1).

187b) (E)-3-[5-(4-chloro-phenyl)-pyridin-2-yl]-N-(4-methylaminomethyl-phenyl)-acrylamide

Prepared analogously to Example 178b starting from tert-butyl (4-{(E)-3-[5-(4-chloro-phenyl)-pyridin-2-yl]-acryloylamino}-benzyl)-methyl-carbaminate. The product was obtained as the trifluoroacetate salt.

Yield: 0.500 g (81% of theory)

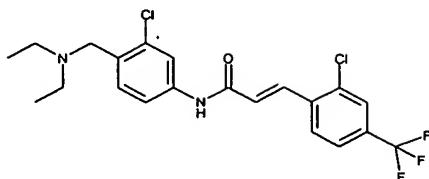
$C_{22}H_{20}ClN_3O * C_2HF_3O_2$ ($M = 491.901$)

Calc.: molpeak ($M+H$) $^+$: 378/380

25 Found: molpeak ($M+H$) $^+$: 278/380 (Cl)

R_f value: 0.30 (silica gel, dichloromethane / MeOH / conc. aqueous ammonia 90:10:0.1).

Example 188:



188) (E)-N-(3-chloro-4-diethylaminomethyl-phenyl)-3-(2-chloro-4-trifluoromethyl-phenyl)-acrylamide

5 Prepared analogously to Example 143 starting from (E)-3-(2-chloro-4-trifluoromethyl-phenyl)-acrylic acid (Z37b) and 3-chloro-4-diethylaminomethyl-phenylamine (Z35b). The crude product was purified by column chromatography (Alox, neutral, act. II-III, petroleum ether / EtOAc 3:1).

Yield: 0.192 g (43% of theory)

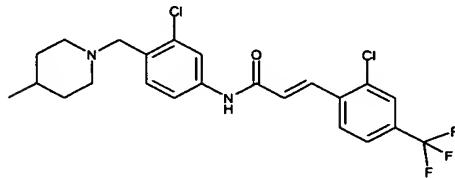
10 C₂₁H₂₁Cl₂F₃N₂O (M= 445.316)

Calc.: molpeak (M+H)⁺: 445/447/449

Found: molpeak (M+H)⁺: 445/447/449 (Cl₂)

R_f value: 0.53 (Alox, petroleum ether / EtOAc 3:1).

15 Example 189:



189) (E)-N-[3-chloro-4-(4-methyl-piperidin-1-ylmethyl)-phenyl]-3-(2-chloro-4-trifluoromethyl-phenyl)-acrylamide

Prepared analogously to Example 143 starting from (E)-3-(2-chloro-4-trifluoromethyl-phenyl)-acrylic acid (Z37b) and 3-chloro-4-(4-methyl-piperidin-1-ylmethyl)-phenylamine (Z36b). The crude product was purified by column chromatography (Alox, neutral, act. II-III, petroleum ether / EtOAc 3:1).

Yield: 0.176 g (37% of theory)

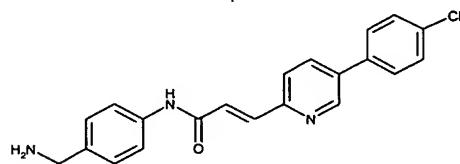
C₂₃H₂₃Cl₂F₃N₂O (M= 471.354)

25 Calc.: molpeak (M+H)⁺: 471/473/475

Found: molpeak (M+H)⁺: 471/473/475 (Cl₂)

R_f value: 0.47 (Alox, dichloromethane / MeOH 50:1).

Example 190:



5

190a) tert-butyl (4-{(E)-3-[5-(4-chloro-phenyl)-pyridin-2-yl]-acryloylamino}-benzyl)-carbaminate

Prepared analogously to Example 182 starting from tert-butyl (E)-3-[5-(4-chloro-phenyl)-pyridin-2-yl]-acrylic acid (Z34b) and (4-amino-benzyl)-methyl-carbaminate (Z33b). The crude product was stirred with MeOH, the precipitate was filtered off and dried in a HV.

Yield: 0.610 g (88% of theory)

C₂₆H₂₆CIN₃O₃ (M= 463.968)

Calc.: molpeak (M+H)⁺: 464/466

15 Found: molpeak (M+H)⁺: 464/466 (Cl)

R_f value: 0.60 (silica gel, dichloromethane / MeOH 9:1).

190b) (E)-N-(4-aminomethyl-phenyl)-3-[5-(4-chloro-phenyl)-pyridin-2-yl]-

20 acrylamide

Prepared analogously to Example 178 starting from tert-butyl (4-{(E)-3-[5-(4-chloro-phenyl)-pyridin-2-yl]-acryloylamino}-benzyl)-carbaminate (Example 186).

The product was obtained as the trifluoroacetate salt.

Yield: 0.600 g (99% of theory)

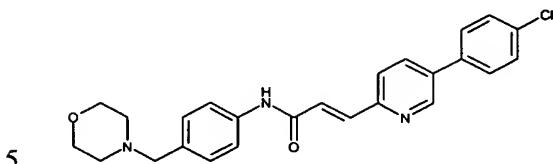
25 C₂₁H₁₈CIN₃O * C₂HF₃O₃ (M= 477.874)

Calc.: molpeak (M-H)⁻: 362/364

Found: molpeak (M-H)⁻: 362/364 (Cl)

R_f value: 0.40 (silica gel, dichloromethane / MeOH / conc. aqueous ammonia 90:10:0.1).

Example 191:



191) (E)-3-[5-(4-chloro-phenyl)-pyridin-2-yl]-N-(4-morpholin-4-ylmethyl-phenyl)-acrylamide

80 μ L (0.930 mmol) morpholine was added to a solution of 0.130 g (0.310 mmol) (E)-N-(4-chloromethyl-phenyl)-3-[5-(4-chloro-phenyl)-pyridin-2-yl]-acrylamide

10 (Z38b) in 20 mL THF and the mixture was stirred for 5 h at 50 °C and 5 h at 75 °C. A further 200 μ L of morpholine were added and the mixture was stirred for 5 h at 70 °C. The reaction mixture was evaporated down i. vac. and the residue was purified by column chromatography (silica gel, dichloromethane / MeOH / conc. aqueous ammonia 90:10:0.1). The product was stirred with ether, the precipitate

15 was filtered off and dried i. vac. at 70 °C.

Yield: 80 mg (60% of theory)

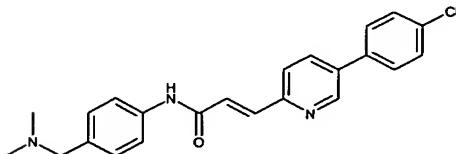
C₂₅H₂₄ClN₃O₂ (M= 433.942)

Calc.: molpeak (M+H)⁺: 434/436

Found: molpeak (M+H)⁺: 434/436 (Cl)

20 R_f value: 0.50 (silica gel, dichloromethane / MeOH 9:1).

Example 192:



25 192) (E)-3-[5-(4-chloro-phenyl)-pyridin-2-yl]-N-(4-dimethylaminomethyl-phenyl)-acrylamide

Prepared analogously to Example 181 starting from (E)-N-(4-aminomethyl-phenyl)-3-[5-(4-chloro-phenyl)-pyridin-2-yl]-acrylamide (Example 190).

Yield: 0.120 g (56% of theory)

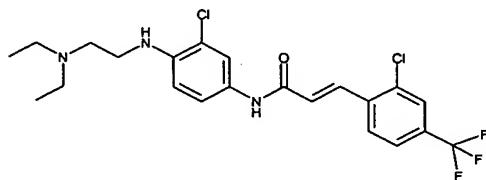
$C_{23}H_{22}ClN_3O$ ($M= 391.904$)

5 Calc.: molpeak ($M+H$)⁺: 392/394

Found: molpeak ($M+H$)⁺: 392/394 (Cl)

R_f value: 0.30 (silica gel, dichloromethane / MeOH / conc. aqueous ammonia 90:10:0.1).

10 Example 193:



193) (E)-N-[3-chloro-4-(2-diethylamino-ethylamino)-phenyl]-3-(2-chloro-4-trifluoromethyl-phenyl)-acrylamide

Prepared in DMF analogously to Example 143 starting from (E)-3-(2-chloro-4-trifluoromethyl-phenyl)-acrylic acid (Z37b) and 2-chloro-*N'*-(2-diethylamino-ethyl)-benzene-1,4-diamine (Z42b). The crude product was purified by column chromatography (Alox, neutral, act. II-III, dichloromethane / MeOH 49:1) and by trituration in ether/petroleum ether.

Yield: 0.215 g (45% of theory)

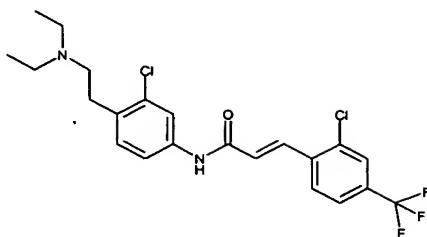
20 $C_{22}H_{24}Cl_2F_3N_3O$ ($M= 474.357$)

Calc.: molpeak ($M+H$)⁺: 474/476/478

Found: molpeak ($M+H$)⁺: 474/476/478 (Cl₂)

R_f value: 0.58 (Alox, dichloromethane / MeOH 49:1).

Example 194:



194) (E)-N-[3-chloro-4-(2-diethylamino-ethyl)-phenyl]-3-(2-chloro-4-trifluoromethyl-phenyl)-acrylamide

5 Prepared in DMF analogously to Example 143 starting from (E)-3-(2-chloro-4-trifluoromethyl-phenyl)-acrylic acid (Z37b) and 3-chloro-4-(2-diethylamino-ethyl)-phenylamine (Z44d). The reaction mixture was poured onto ice water, the precipitate was filtered off, washed with water and dried in a HV. The residue was triturated with ether , the precipitate was filtered off, washed with ether and dried in
10 a HV.

Yield: 0.278 g (60% of theory)

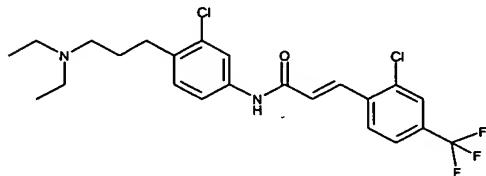
$C_{22}H_{23}Cl_2F_3N_2O$ ($M= 459.343$)

Calc.: molpeak $(M+H)^+$: 459/461/463

Found: molpeak $(M+H)^+$: 459/461/463 (Cl_2)

15 R_f value: 0.32 (Alox, petroleum ether / EtOAc 1:1).

Example 195:



195) (E)-N-[3-chloro-4-(3-diethylamino-propyl)-phenyl]-3-(2-chloro-4-

20 trifluoromethyl-phenyl)-acrylamide

A solution of 0.290 g (0.603 mmol) (E)-N-[4-(3-bromo-propyl)-3-chloro-phenyl]-3-(2-chloro-4-trifluoromethyl-phenyl)-acrylamide (Z45d) in 2 mL diethylamine was heated to 100 °C in a sealed reaction vessel in the microwave for 5 min.. The reaction mixture was diluted with EtOAc , the org. phase was washed with water,

dried over sodium sulphate and evaporated down i. vac. . The residue was triturated with ether, the precipitate was filtered off, washed with ether and dried in a HV.

Yield: 0.180 g (63% of theory)

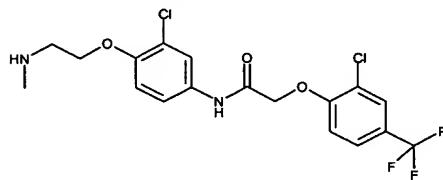
5 C₂₃H₂₅Cl₂F₃N₂O (M= 473.370)

Calc.: molpeak (M+H)⁺: 473/475/477

Found: molpeak (M+H)⁺: 473/475/477 (Cl₂)

R_f value: 0.33 (Alox, dichloromethane / MeOH 30:1).

10 Example 196:



196a) N-[4-(N-tert.butoxycarbonyl-2-methylamino-ethoxy)-3-chloro-phenylamine]-2-(2-chloro-4-trifluoromethyl-phenoxy)-acetamide

The product was prepared analogously to Example 143 from 260 mg (1.00 mmol)

15 (2-chloro-4-trifluoromethyl-phenoxy)-acetic acid (Z2b), 0.120 mL(1.10 mmol) N-methylmorpholine, 0.140 mL (1.10 mmol) isobutyl chloroformate and 330 mg (1.10 mmol) 4-(N-tert.butoxycarbonyl-2-methylamino-ethoxy)-3-chloro-phenylamine (Z40b).

Yield: 0.54 g (100% of theory)

20 C₂₃H₂₅Cl₂F₃N₂O₅ (M= 537.36)

Calc.: molpeak (M-H)⁻: 535/537/539

Found: molpeak (M-H)⁻: 535/537/539 (Cl₂)

R_f value: 0.75 (silica gel, dichloromethane/methanol 19:1)

25 196b) N-[4-(2-methylamino-ethoxy)-3-chloro-phenylamine]-2-(2-chloro-4-trifluoromethyl-phenoxy)-acetamide

The product was obtained analogously to Example 115 from 560 mg (1.04 mmol) N-[4-(N-tert.butoxycarbonyl-2-methylamino-ethoxy)-3-chloro-phenylamine]-2-(2-chloro-4-trifluoromethyl-phenoxy)-acetamide.

Yield: 0.43 g (94% of theory)

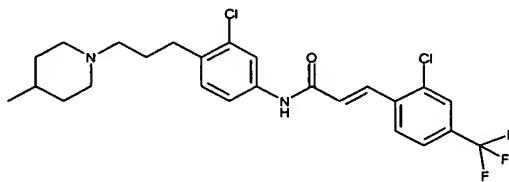
5 C₁₈H₁₇Cl₂F₃N₂O₃ (M= 437.24)

Calc.: molpeak (M+H)⁺: 437/439/441

Found: molpeak (M+H)⁺: 437/439/441

R_f value: 0.35 (silica gel, dichloromethane / MeOH 9:1)

10 Example 197:



197) 2-(2-chloro-4-trifluoromethyl-phenoxy)-N-[4-(2-diethylamino-ethoxy)-3-methyl-phenyl]-acetamide

0.290 g (0.603 mmol) (E)-N-[4-(3-bromo-propyl)-3-chloro-phenyl]-3-(2-chloro-4-

15 trifluoromethyl-phenyl)-acrylamide (Z45d) and 0.270 g (2.614 mmol) 4-methylpiperidine was heated to 100 °C in a sealed reaction vessel in the microwave for 5 min..

The reaction mixture was diluted with EtOAc , the precipitate formed was filtered off, stirred with 1 N aqueous NaOH solution, washed with water and dried in a HV.

20 Yield: 0.280 g (93% of theory)

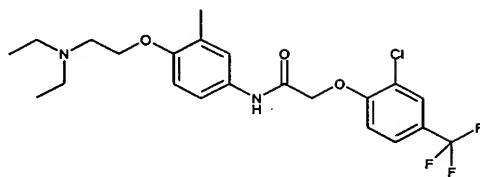
C₂₅H₂₇Cl₂F₃N₂O (M= 499.408)

Calc.: molpeak (M+H)⁺: 499/501/503

Found: molpeak (M+H)⁺: 499/501/503 (Cl₂)

R_f value: 0.33 (Alox, dichloromethane / MeOH 30:1).

Example 198:



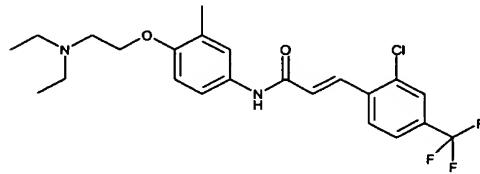
198) N-[4-(2-diethylaminoethoxy)-3-methyl-phenyl]-2-(2-chloro-4-trifluoromethyl-phenoxy)-acetamide

5 The product was prepared according to general working method I from 100 mg (0.40 mmol) (2-chloro-4-trifluoromethyl-phenoxy)-acetic acid (Z2b) and 100 mg (0.44 mmol) 4-(2-diethylaminoethoxy)-3-methyl-phenylamine (Z39b). The product was obtained as the formate salt.

Yield: 51 mg (25% of theory)

10 C₂₂H₂₆ClF₃N₂O₃ (M= 458.91)
Calc.: molpeak (M+H)⁺: 459/461
Found: molpeak (M+H)⁺: 459/461
R_f value: 0.4 (silica gel, dichloromethane / MeOH 9:1)

15 Example 199:



199) (E)-N-[4-(2-diethylaminoethoxy)-3-methyl-phenyl]-2-(2-chloro-4-trifluoromethyl-phenoxy)-acrylamide

The product was prepared analogously to Example 119 from 100 mg (0.40 mmol)

20 (E)-3-(2-chloro-4-trifluoromethyl-phenyl)-acrylic acid (Z37b) and 100 mg (0.44 mmol) 4-(2-diethylaminoethoxy)-3-methyl-phenylamine (Z39b). The product was obtained as the formate salt.

Yield: 44 mg (22% of theory)

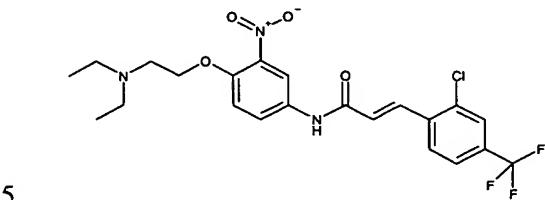
C₂₃H₂₆ClF₃N₂O₂ (M= 454.92)

25 Calc.: molpeak (M+H)⁺: 454/456

Found: molpeak (M+H)⁺: 455/456

R_f value: 0.2 (silica gel, dichloromethane / MeOH 9:1)

Example 200:



200) (E)-3-(2-chloro-4-trifluoromethyl-phenyl)-N-[4-(2-diethylamino-ethoxy)-3-nitro-phenyl]-acrylamide

The product was prepared analogously to Example 119 from 100 mg (0.40 mmol) (E)-3-(2-chloro-4-trifluoromethyl-phenyl)-acrylic acid (Z37b) and 110 mg (0.44 mmol) 4-(2-diethylamino-ethoxy)-3-nitro-phenylamine (Z31a). The product was obtained as the formate salt.

Yield: 27 mg (13% of theory)

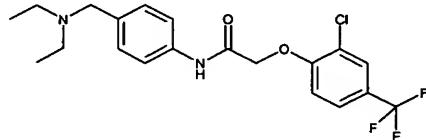
C₂₂H₂₃ClF₃N₃O₄ (M= 485.89)

Calc.: molpeak (M+H)⁺: 485/487

15 Found: molpeak (M+H)⁺: 486/488

R_f value: 0.3 (silica gel, dichloromethane / MeOH 9:1)

Example 201:



20 201) N-(4-diethylaminomethyl-phenyl)-2-(2-chloro-4-trifluoromethyl-phenoxy)-acetamide

The product was prepared according to general working method I from 100 mg (0.40 mmol) (2-chloro-4-trifluoromethyl-phenoxy)-acetic acid (Z2b) and 80 mg (0.44 mmol) 4-diethylaminomethyl-phenylamine (for preparation see WO 01/27081). The product was obtained as the formate salt.

Yield: 92 mg (50% of theory)

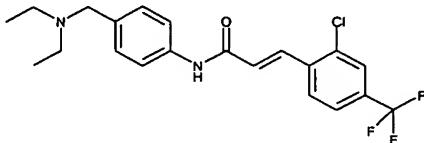
$C_{20}H_{22}ClF_3N_2O_2$ ($M= 414.85$)

Calc.: molpeak ($M+H$) $^+$: 414/416

Found: molpeak ($M+H$) $^+$: 415/417

5 R_f value: 0.25 (silica gel, dichloromethane / MeOH 9:1)

Example 202:



202) (E)-N-(4-diethylaminomethyl-phenyl)-2-(2-chloro-4-trifluoromethyl-phenoxy)-

10 acrylamide

The product was prepared analogously to Example 119 from 100 mg (0.40 mmol) (E)-3-(2-chloro-4-trifluoromethyl-phenyl)-acrylic acid (Z37b) and 80 mg (0.44 mmol) 4-diethylaminomethyl-phenylamine (for preparation see WO 01/27081). The product was obtained as the formate salt.

15 Yield: 27 mg (15% of theory)

$C_{21}H_{22}ClF_3N_2O$ ($M= 410.87$)

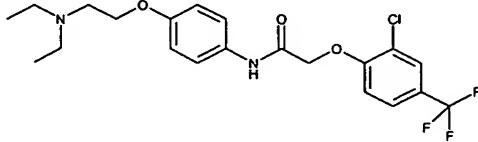
Calc.: molpeak ($M+H$) $^+$: 410/412

Found: molpeak ($M+H$) $^+$: 411/413

R_f value: 0.15 (silica gel, dichloromethane / MeOH 9:1)

20

Example 203:



203) N-[4-(2-diethylamino-ethoxy)-phenyl]-2-(2-chloro-4-trifluoromethyl-phenoxy)-

acetamide

25 The product was prepared according to general working method I from 100 mg (0.40 mmol) (2-chloro-4-trifluoromethyl-phenoxy)-acetic acid (Z2b) and 90 mg

(0.44 mmol) 4-(2-diethylamino-ethoxy)-phenylamine (Z5b). The product was obtained as the formate salt.

Yield: 45 mg (23% of theory)

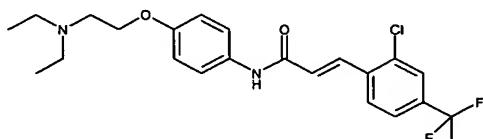
$C_{21}H_{24}ClF_3N_2O_3$ ($M= 444.88$)

5 Calc.: molpeak ($M+H$)⁺: 444/446

Found: molpeak ($M+H$)⁺: 445/447

R_f value: 0.3 (silica gel, dichloromethane / MeOH 9:1)

Example 204:



10

204) (E)-N-[4-(2-diethylamino-ethoxy)-phenyl]-2-(2-chloro-4-trifluoromethyl-phenoxy)-acrylamide

The product was prepared analogously to Example 119 from 100 mg (0.40 mmol)

(E)-3-(2-chloro-4-trifluoromethyl-phenyl)-acrylic acid (Z37b) and 90 mg (0.44

15 mmol) 4-(2-diethylamino-ethoxy)-phenylamine (Z5b). The product was obtained as the formate salt.

Yield: 35 mg (18% of theory)

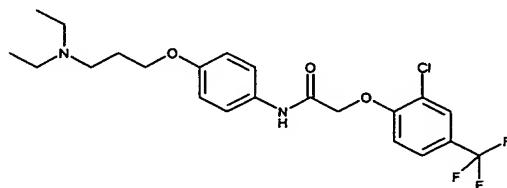
$C_{22}H_{24}ClF_3N_2O_2$ ($M= 440.89$)

Calc.: molpeak ($M+H$)⁺: 440/442

20 Found: molpeak ($M+H$)⁺: 441/443

R_f value: 0.2 (silica gel, dichloromethane / MeOH 9:1)

Example 205:

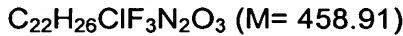


205) N-[4-(3-diethylamino-propyloxy)-phenyl]-2-(2-chloro-4-trifluoromethyl-phenoxy)-acetamide

The product was prepared according to general working method I from 100 mg (0.40 mmol) (2-chloro-4-trifluoromethyl-phenoxy)-acetic acid (Z2b) and 100 mg

5 (0.44 mmol) 4-(3-diethylamino-propyloxy)-phenylamine (for preparation see WO 99/52869). The product was obtained as the formate salt.

Yield: 48 mg (23.8% of theory)

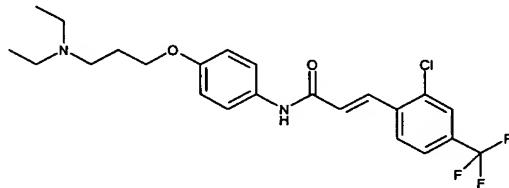


Calc.: molpeak ($M+H$)⁺: 458/460

10 Found: molpeak ($M+H$)⁺: 459/61

R_f value: 0.40 (silica gel, dichloromethane / MeOH 9:1)

Example 206:

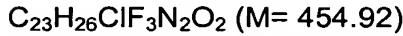


15 206) (E)-N-[4-(3-diethylamino-propyloxy)-phenyl]-2-(2-chloro-4-trifluoromethyl-phenoxy)-acrylamide

The product was prepared analogously to Example 119 from 100 mg (0.40 mmol) (E)-3-(2-chloro-4-trifluoromethyl-phenyl)-acrylic acid (Z37b) and 100 mg (0.44 mmol) 4-(3-diethylamino-propyloxy)-phenylamine (for preparation see WO

20 99/52869). The product was obtained as the formate salt.

Yield: 33 mg (16% of theory)

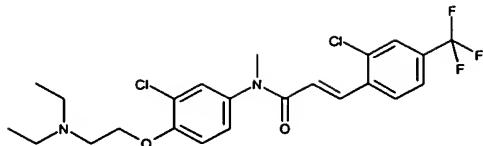


Calc.: molpeak ($M+H$)⁺: 454/456

Found: molpeak ($M+H$)⁺: 455/7

25 R_f value: 0.39 (silica gel, dichloromethane / MeOH 9:1)

Example 207:



207) (E)-N-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-N-methyl-2-(2-chloro-4-trifluoromethyl-phenoxy)-acrylamide

5 The product was prepared analogously to Example 119 from 100 mg (0.40 mmol) (E)-3-(2-chloro-4-trifluoromethyl-phenyl)-acrylic acid (Z37b) and 110 mg (0.44 mmol) N-[3-chloro-4-(2-diethylamino-ethoxy)-phenyl]-methylamine (Z125b). The product was obtained as the formate salt.

Yield: 38 mg (18% of theory)

10 $C_{23}H_{25}Cl_2F_3N_2O_2$ ($M = 489.36$)

Calc.: molpeak $(M+H)^+$: 487/489/491

Found: molpeak $(M+H)^+$: 489/91/93

R_f value: 0.48 (silica gel, dichloromethane / MeOH 9:1)

15 Example 208:



208) (E)-N-{4-[N-(2-dimethylamino-ethyl)-N-methyl-amino]-phenyl}-2-(2-chloro-4-trifluoromethyl-phenoxy)-acrylamide

The product was prepared analogously to Example 119 from 100 mg (0.40 mmol)

20 (E)-3-(2-chloro-4-trifluoromethyl-phenyl)-acrylic acid (Z37b) and 90 mg (0.44 mmol) N-(2-dimethylamino-ethyl)-N-methyl-benzene-1,4-diamine (Z141b). The product was obtained as the formate salt.

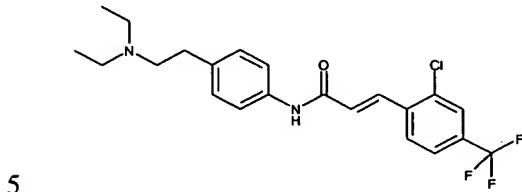
Yield: 34 mg (18% of theory)

$C_{21}H_{23}ClF_3N_3O$ ($M = 425.88$)

25 Calc.: molpeak $(M+H)^+$: 425/427

Found: molpeak (M+H)⁺: 426/8
 R_f value: 0.29 (silica gel, dichloromethane / MeOH 9:1)

Example 209:



209) (E)-N-[4-(2-diethylamino-ethyl)-phenyl]-2-(2-chloro-4-trifluoromethyl-phenoxy)-acrylamide

The product was prepared analogously to Example 119 from 100 mg (0.40 mmol) (E)-3-(2-chloro-4-trifluoromethyl-phenyl)-acrylic acid (Z37b) and 90 mg (0.44 mmol) 4-(2-diethylamino-ethyl)-phenylamine (for preparation see WO 01/27081).
10 The product was obtained as the formate salt.

Yield: 27 mg (14% of theory)

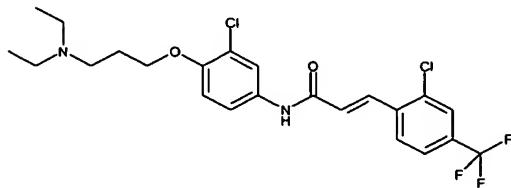
$C_{22}H_{24}ClF_3N_2O$ ($M = 424.89$)

Calc.: molpeak (M+H)⁺: 424/426

15 Found: molpeak (M+H)⁺: 425/27

R_f value: 0.30 (silica gel, dichloromethane / MeOH 9:1)

Example 210:



20 210) (E)-N-[3-chloro-4-(3-diethylamino-propyloxy)-phenyl]-2-(2-chloro-4-trifluoromethyl-phenoxy)-acrylamide

The product was prepared analogously to Example 119 from 100 mg (0.40 mmol) (E)-3-(2-chloro-4-trifluoromethyl-phenyl)-acrylic acid (Z37b) and 110 mg (0.44

mmol) 3-chloro-4-(3-diethylamino-propyloxy)-phenylamine (Z29b). The product was obtained as the formate salt.

Yield: 38 mg (18% of theory)

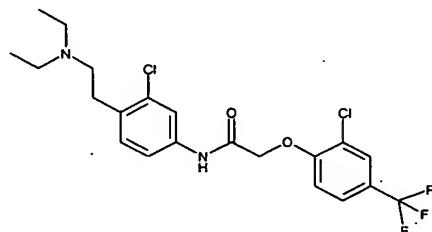
$C_{23}H_{25}Cl_2F_3N_2O_2$ ($M= 489.36$)

5 Calc.: molpeak $(M+H)^+$: 489/491

Found: molpeak $(M+H)^+$: 489/91/93

R_f value: 0.36 (silica gel, dichloromethane / MeOH 9:1)

Example 211:



10

211) N-[3-chloro-4-(2-diethylamino-ethyl)-phenyl]-2-(2-chloro-4-trifluoromethyl-phenoxy)-acetamide

Prepared analogously to Example 143 starting from (2-chloro-4-trifluoromethyl-phenoxy)-acetic acid (Z2b) and 3-chloro-4-(2-diethylamino-ethyl)-phenylamine

15 (Z44d). The reaction mixture was poured onto ice water and the aqueous phase was extracted with EtOAc. The org. phase was dried over sodium sulphate and evaporated down i. vac. The residue was purified by column chromatography (Alox, neutral, act. II-III, gradient petroleum ether / EtOAc 5:2 → 1:1).

Yield: 0.258 g (65% of theory)

20 $C_{21}H_{23}Cl_2F_3N_2O_2$ ($M= 463.331$)

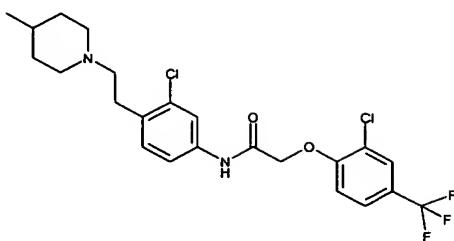
Calc.: molpeak $(M+H)^+$: 463/465/467

Found: molpeak $(M+H)^+$: 463/465/467 (Cl_2)

R_f value: 0.46 (Alox, petroleum ether / EtOAc 1:1)

25

Example 212:



212) N-(3-chloro-4-[2-(4-methyl-piperidin-1-yl)-ethyl]-phenyl)-2-(2-chloro-4-trifluoromethyl-phenoxy)-acetamide

5 Prepared analogously to Example 143 starting from (2-chloro-4-trifluoromethyl-phenoxy)-acetic acid (Z2b) and 3-chloro-4-[2-(4-methyl-piperidin-1-yl)-ethyl]-phenylamine (Z46c). The reaction mixture was poured onto ice water and the aqueous phase was extracted with EtOAc. The org. phase was dried over sodium sulphate and evaporated down i. vac. The residue was purified by column chromatography (Alox, neutral, act. II-III, gradient petroleum ether / EtOAc 3:1 → 1:1).

10 Yield: 0.218 g (52% of theory)

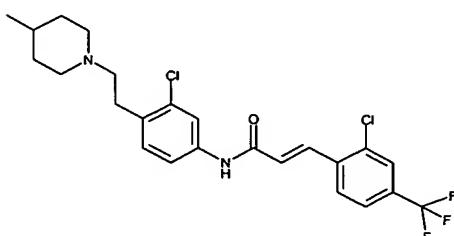
$C_{23}H_{25}Cl_2F_3N_2O_2$ ($M = 489.369$)

Calc.: molpeak ($M+H$) $^+$: 489/491/493

15 Found: molpeak ($M+H$) $^+$: 489/491/493 (Cl_2)

R_f value: 0.46 (Alox, petroleum ether / EtOAc 1:1)

Example 213:



20

213) (E)-N-(3-chloro-4-[2-(4-methyl-piperidin-1-yl)-ethyl]-phenyl)-3-(2-chloro-4-trifluoromethyl-phenyl)-acrylamide

Prepared in DMF analogously to Example 143 starting from (E)-3-(2-chloro-4-trifluoromethyl-phenyl)-acrylic acid (Z37b) and 3-chloro-4-[2-(4-methyl-piperidin-1-yl)-ethyl]-phenylamine (Z46c). The crude product was purified by column chromatography (Alox, neutral, act. II-III, gradient petroleum ether / EtOAc 3:1 → 2:1) and then triturated with petroleum ether.

Yield: 0.240 g (51% of theory)

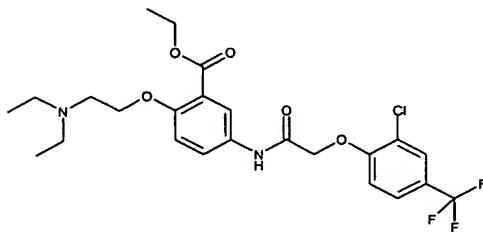
$C_{24}H_{25}Cl_2F_3N_2O$ ($M= 485.381$)

Calc.: molpeak ($M+H$) $^+$: 485/487/489

Found: molpeak ($M+H$) $^+$: 485/487/489 (Cl_2)

10 R_f value: 0.38 (Alox, petroleum ether / EtOAc 1:1)

Example 214:



214) ethyl 5-[2-(2-chloro-4-trifluoromethyl-phenoxy)-acetylamo] -2-(2-diethylaminoethoxy)benzoate

15 Prepared analogously to Example 143 starting from (2-chloro-4-trifluoromethyl-phenoxy)-acetic acid (Z2b) and ethyl 5-amino-2-(2-diethylaminoethoxy)-benzoate. The reaction mixture was evaporated down i. vac. and the residue was dissolved in dichloromethane. The org. phase was washed with water, dried over sodium sulphate and evaporated down i. vac. . Purification by column chromatography (Alox, neutral, act. II-III, gradient petroleum ether / EtOAc 70:30 → 50:50) yielded the product.

20 Yield: 1.220 g (59% of theory)

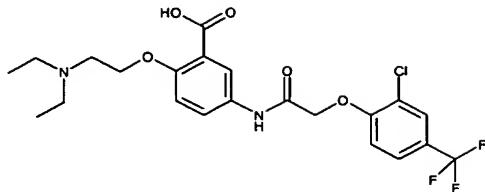
$C_{24}H_{28}ClF_3N_2O_5$ ($M= 516.949$)

25 Calc.: molpeak ($M+H$) $^+$: 517/519

Found: molpeak ($M+H$) $^+$: 517/519 (Cl)

R_f value: 0.62 (Alox, petroleum ether / EtOAc 2:1)

Example 215:



215) 5-[2-(2-chloro-4-trifluoromethyl-phenoxy)-acetylamino]-2-(2-diethylamino-
5 ethoxy)-benzoic acid

4.00 mL 1 M aqueous NaOH solution was added to a solution of 1.00 g (1.934 mmol) ethyl 5-[2-(2-chloro-4-trifluoromethyl-phenoxy)-acetylamino]-2-(2-diethylaminoethoxy)-benzoate in 30 mL EtOH and the mixture was stirred for 3 h at RT. 4.00 mL 1 M aqueous HCl was added and again the mixture was stirred for
10 1 h. The reaction mixture was evaporated down i. vac. , combined with water and the precipitate was filtered off.

Yield: 0.220 g (23% of theory)

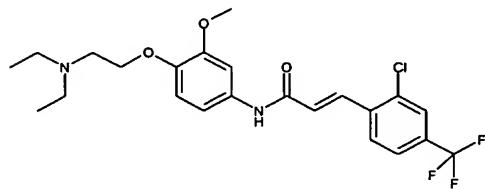
$C_{22}H_{24}ClF_3N_2O_5$ ($M= 488.895$)

Calc.: molpeak ($M+H$)⁺: 487/489

15 Found: molpeak ($M+H$)⁺: 487/489 (Cl)

R_f value: 0.36 (silica gel, dichloromethane / MeOH 9:1)

Example 216:



20 216) (E)-3-(2-chloro-4-trifluoromethyl-phenyl)-N-[4-(2-diethylaminoethoxy)-3-methoxy-phenyl]-acrylamide

The product was prepared according to general working method I starting from 0.100 g (0.400 mmol) (E)-3-(2-chloro-4-trifluoromethyl-phenyl)-acrylic acid (Z37b) and 0.121 g (0.440 mmol) 4-(2-diethylaminoethoxy)-3-methoxy-phenylamine. The

crude product was purified by HPLC (Stable Bond C18; 3.5 μm ; water / acetonitrile / formic acid 9:1:0.01 \rightarrow 1:9:0.01 over 9 min) and the product was obtained as the formate salt.

Yield: 41 mg (20% of theory)

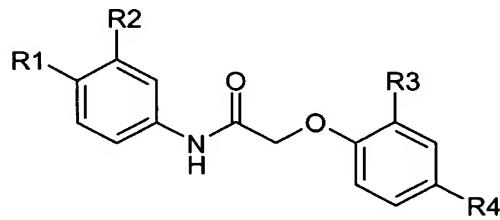
5 $\text{C}_{23}\text{H}_{26}\text{ClF}_3\text{N}_2\text{O}_3 * \text{CH}_2\text{O}_2$ ($M = 516.949$)

Calc.: molpeak $(\text{M}+\text{H})^+$: 471/473

Found: molpeak $(\text{M}+\text{H})^+$: 471/473 (Cl)

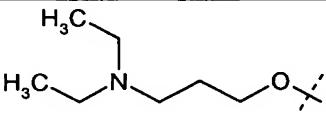
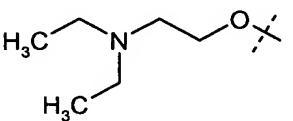
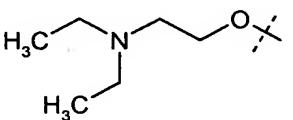
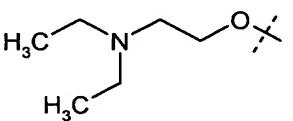
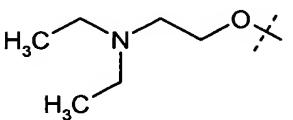
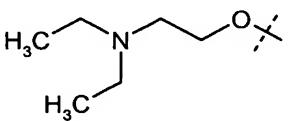
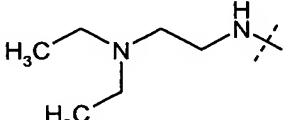
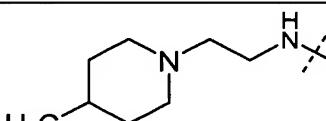
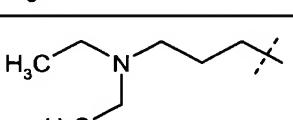
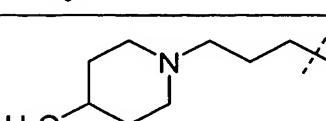
R_f value: 0.35 (silica gel, dichloromethane / MeOH 9:1)

10 The following compounds may be prepared analogously to the foregoing Examples:

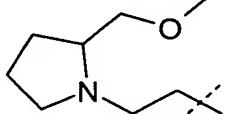
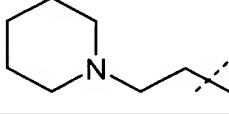
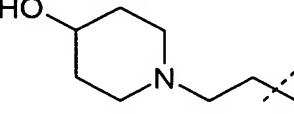
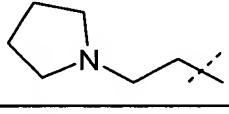
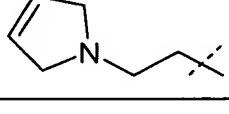
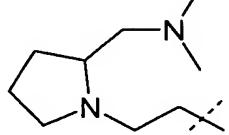
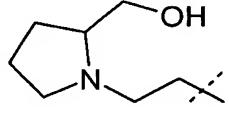
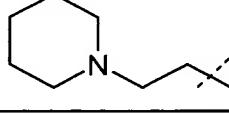
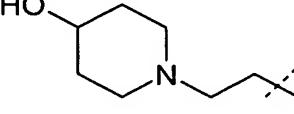
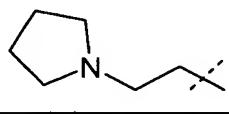
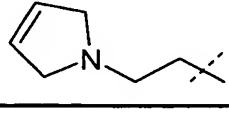


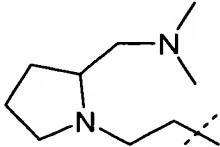
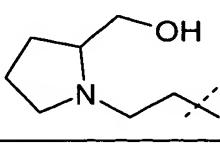
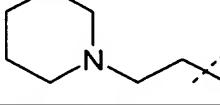
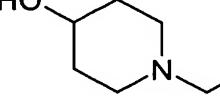
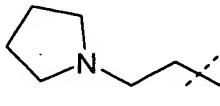
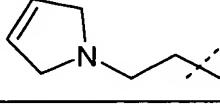
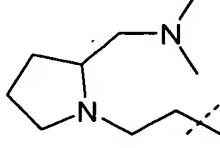
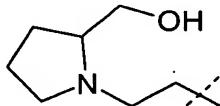
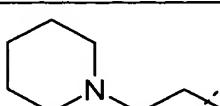
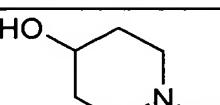
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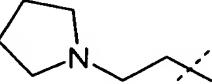
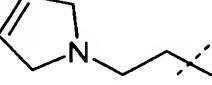
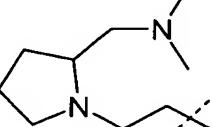
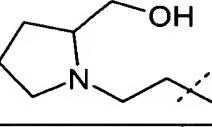
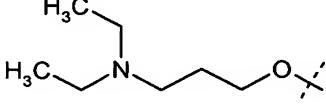
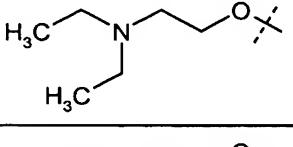
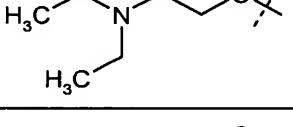
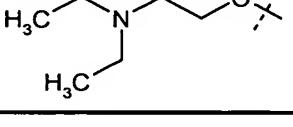
Example	R1	R2	R3	R4
217		-OMe	-Cl	-CF ₃
218		-Br	-Cl	-CF ₃
219		-CN	-Cl	-CF ₃
220		-F	-Cl	-CF ₃

221		-CH ₃	-Cl	-CF ₃
222		-F	-Cl	-CF ₃
223		-F	-Cl	-CF ₃
224		-COOEt	-Cl	-CF ₃
225		-COOH	-Cl	-CF ₃
226		-CONH ₂	-Cl	-CF ₃
227		-Cl	-Cl	-CF ₃
228		-Cl	-Cl	-CF ₃
229		-Cl	-Cl	-CF ₃
230		-Cl	-Cl	-CF ₃

231		-H	-Cl	-CF ₃
232		-H	-Cl	-CF ₃
233		-Cl	-Cl	-CF ₃
234		-Cl	-Cl	-CF ₃
235		-Cl	-Cl	-CF ₃
236		-Cl	-Cl	-CF ₃
237		-Cl	-Cl	-CF ₃
238		-Cl	-Cl	-CF ₃
240		-Cl	-Cl	-CF ₃
241		-Cl	-Cl	-CF ₃

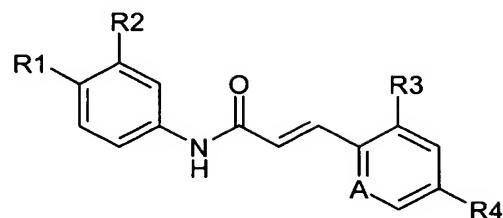
242		-Cl	-Cl	-CF ₃
243		-Br	-Cl	-CF ₃
244		-Br	-Cl	-CF ₃
245		-Br	-Cl	-CF ₃
246		-Br	-Cl	-CF ₃
247		-Br	-Cl	-CF ₃
248		-Br	-Cl	-CF ₃
249		-OMe	-Cl	-CF ₃
250		-OMe	-Cl	-CF ₃
251		-OMe	-Cl	-CF ₃
252		-OMe	-Cl	-CF ₃

253		-OMe	-Cl	-CF ₃
254		-OMe	-Cl	-CF ₃
255		-Cl	-Cl	-Br
256		-Cl	-Cl	-Br
257		-Cl	-Cl	-Br
258		-Cl	-Cl	-Br
259		-Cl	-Cl	-Br
260		-Cl	-Cl	-Br
261		-Cl	-Cl	-Ph
262		-Cl	-Cl	-Ph

263		-Cl	-Cl	-Ph
364		-Cl	-Cl	-Ph
265		-Cl	-Cl	-Ph
266		-Cl	-Cl	-Ph
267		-Cl	-Cl	-Ph
268		-Br	-Cl	-Ph
269		-OMe	-Cl	-Ph
270		-CN	-Cl	-Ph

The following compounds may be prepared analogously to the foregoing

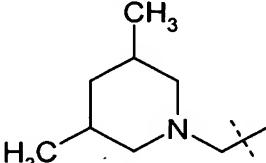
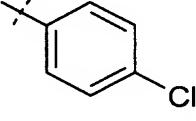
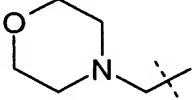
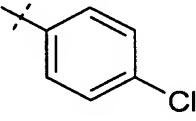
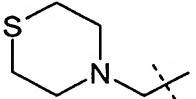
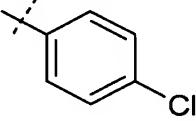
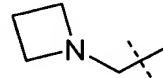
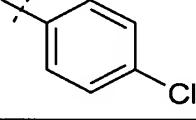
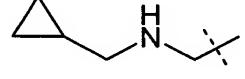
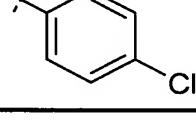
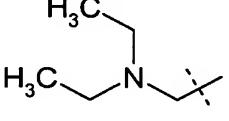
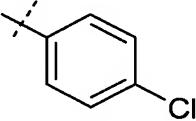
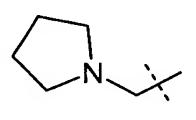
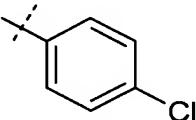
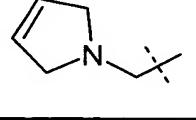
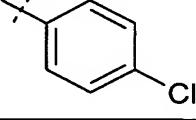
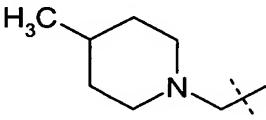
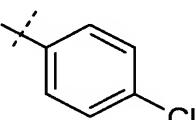
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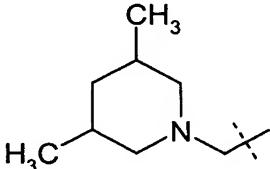
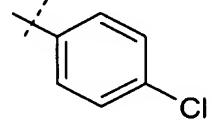
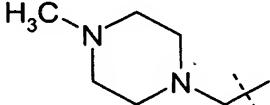
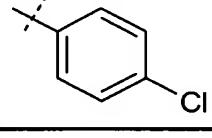
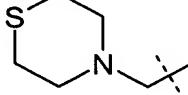
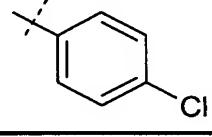
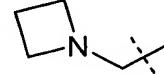
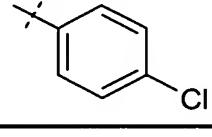
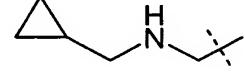
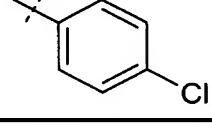
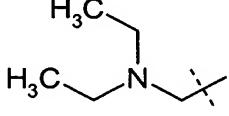
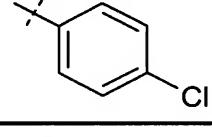
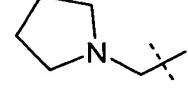
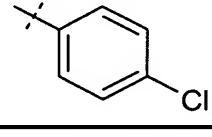
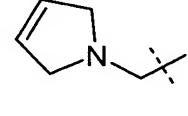
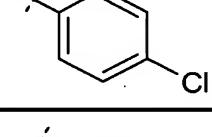
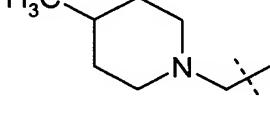
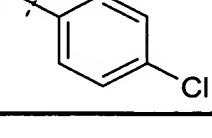


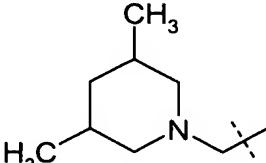
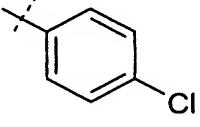
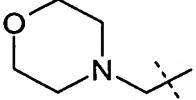
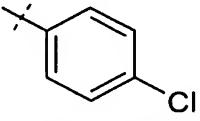
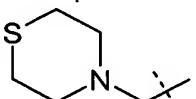
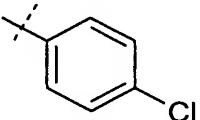
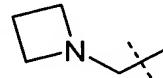
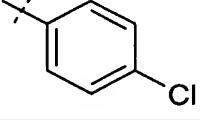
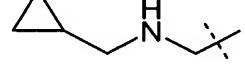
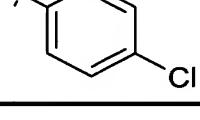
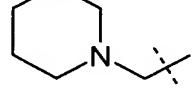
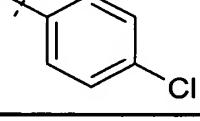
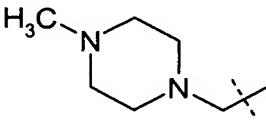
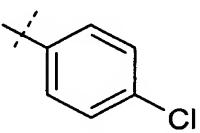
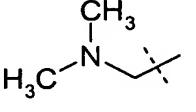
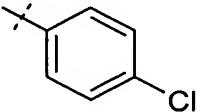
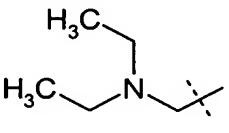
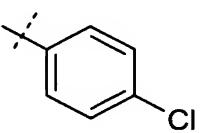
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Number	R1	R2	R3	R4	A
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272		-Br	-Cl	-CF3	CH
273		-CN	-Cl	-CF3	CH
274		-F	-Cl	-CF3	CH
275		-Cl	-Cl	-CF3	CH
276		-Cl	-Cl	-CF3	CH
277		-Cl	-Cl	-CF3	CH
278		-NO2	-Cl	-CF3	CH

279		-COOEt	-Cl	-CF ₃	CH
280		-COOH	-Cl	-CF ₃	CH
281		-CONH ₂	-Cl	-CF ₃	CH
282		-Cl	-Cl	-CF ₃	CH
283		-Cl	-Cl	-CF ₃	CH
284		-Cl	-Cl	-Ph	CH
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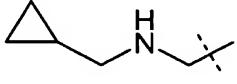
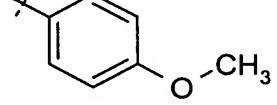
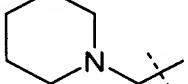
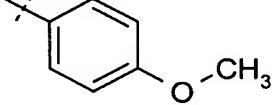
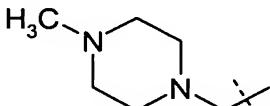
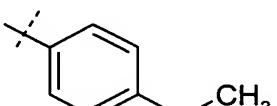
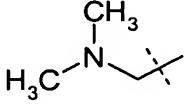
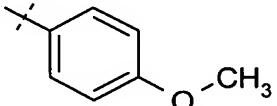
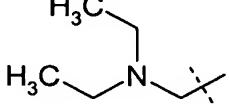
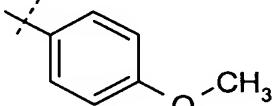
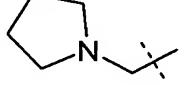
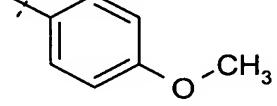
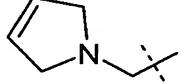
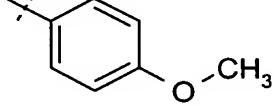
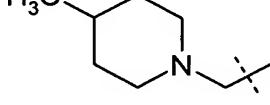
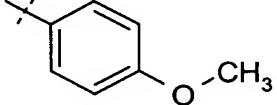
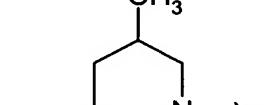
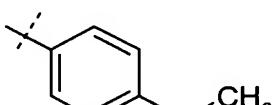
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294		-H	-H		N
295		-H	-H		N
296		-H	-H		N
297		-H	-H		N

298		-H	-H		N
299		-H	-H		N
300		-H	-H		N
301		-H	-H		N
302		-H	-H		N
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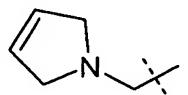
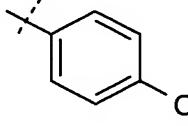
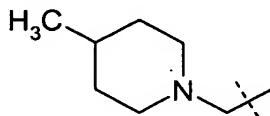
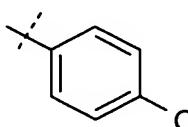
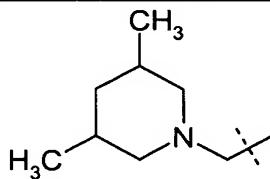
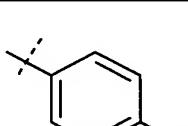
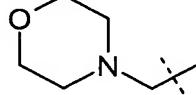
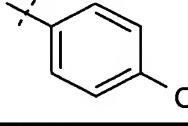
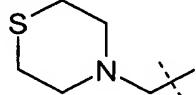
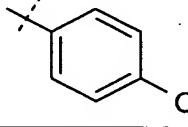
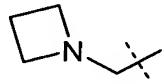
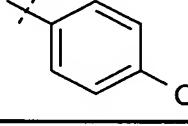
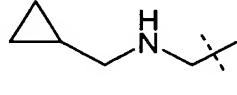
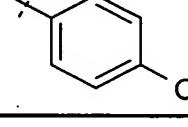
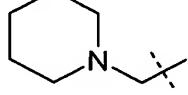
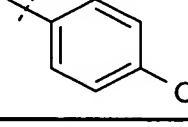
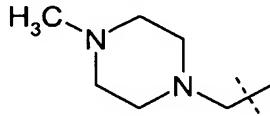
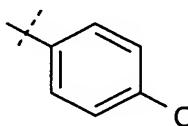
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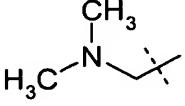
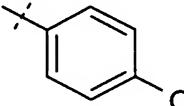
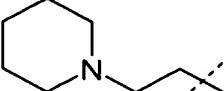
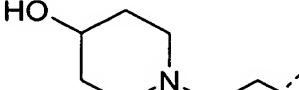
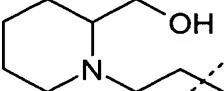
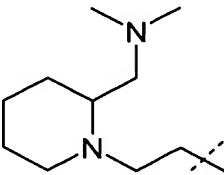
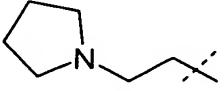
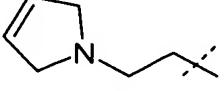
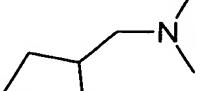
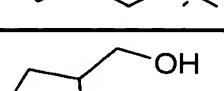
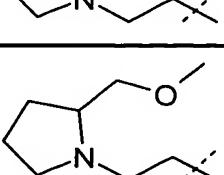
316		-Cl	-H		N
317		-Cl	-H		N
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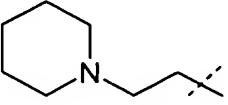
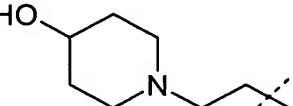
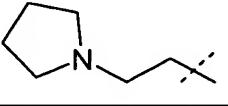
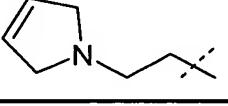
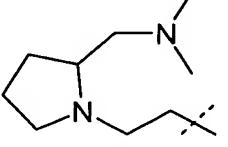
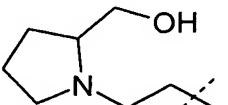
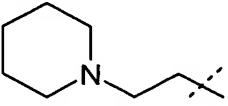
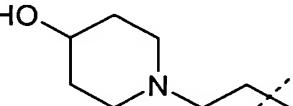
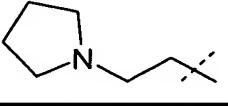
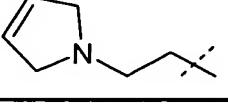
325		-Cl	-H		N
326		-H	-H		CH
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329		-H	-H		CH
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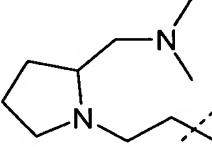
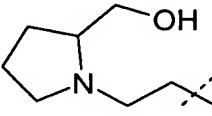
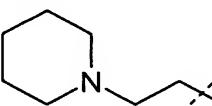
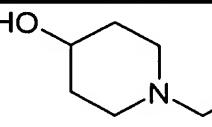
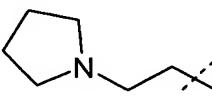
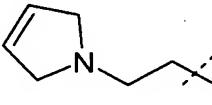
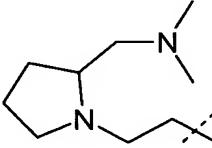
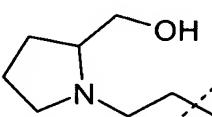
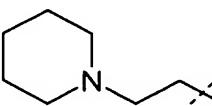
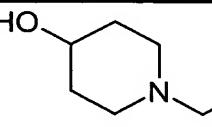
334		-H	-H		CH
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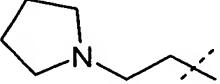
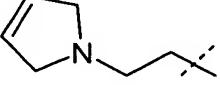
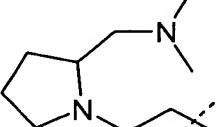
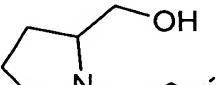
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348		-H	-H		N
349		-H	-H		N
350		-H	-F		CH
351		-H	-F		CH

352		-H	-F		CH
353		-H	-F		CH
354		-H	-F		CH
355		-H	-F		CH
356		-H	-F		CH
357		-H	-F		CH
358		-H	-F		CH
359		-H	-F		CH
360		-H	-F		CH

361		-H	-F		CH
362		-Cl	-Cl		CH
363		-Cl	-Cl		CH
364		-Cl	-Cl		CH
365		-Cl	-Cl		CH
366		-Cl	-Cl		CH
367		-Cl	-Cl		CH
368		-Cl	-Cl		CH
369		-Cl	-Cl		CH
370		-Cl	-Cl		CH

371		-Br	-Cl	-CF ₃	CH
372		-Br	-Cl	-CF ₃	CH
373		-Br	-Cl	-CF ₃	CH
374		-Br	-Cl	-CF ₃	CH
375		-Br	-Cl	-CF ₃	CH
376		-Br	-Cl	-CF ₃	CH
377		-OMe	-Cl	-CF ₃	CH
378		-OMe	-Cl	-CF ₃	CH
379		-OMe	-Cl	-CF ₃	CH
380		-OMe	-Cl	-CF ₃	CH

381		-OMe	-Cl	-CF ₃	CH
382		-OMe	-Cl	-CF ₃	CH
383		-Cl	-Cl	-Ph	CH
384		-Cl	-Cl	-Ph	CH
385		-Cl	-Cl	-Ph	CH
386		-Cl	-Cl	-Ph	CH
387		-Cl	-Cl	-Ph	CH
388		-Cl	-Cl	-Ph	CH
389		-Cl	-H	-Ph	N
390		-Cl	-H	-Ph	N

391		-Cl	-H	-Ph	N
392		-Cl	-H	-Ph	N
393		-Cl	-H	-Ph	N
394		-Cl	-H	-Ph	N

Some test methods for determining an MCH-receptor antagonistic activity will now be described. In addition, other test methods known to the skilled man are used,

5 e.g. by inhibiting the MCH-receptor-mediated inhibition of cAMP production, as described by Hoogduijn M et al. in "Melanin-concentrating hormone and its receptor are expressed and functional in human skin", Biochem. Biophys. Res Commun. 296 (2002) 698-701 and by biosensory measurement of the binding of MCH to the MCH receptor in the presence of antagonistic substances by plasmon

10 resonance, as described by Karlsson OP and Lofas S. in "Flow-Mediated On-Surface Reconstitution of G-Protein Coupled Receptors for Applications in Surface Plasmon Resonance Biosensors", Anal. Biochem. 300 (2002), 132-138. Other methods of testing antagonistic activity to MCH receptors are contained in the references and patent documents mentioned hereinbefore, and the description of

15 the test methods used is hereby incorporated in this application.

MCH-1 receptor binding test

Method: MCH binding to hMCH-1R transfected cells
 Species: Human

Test cell: hMCH-1R stably transfected into CHO/Galpha16 cells

Results: IC50 values

Membranes from CHO/Galpha16 cells stably transfected with human hMCH-1R are resuspended using a syringe (needle 0.6 x 25 mm) and diluted in test buffer

5 (50 mM HEPES, 10 mM MgCl₂, 2 mM EGTA, pH 7.00; 0.1 % bovine serum albumin (protease-free), 0.021 % bacitracin, 1 µg/mL aprotinin, 1 µg/mL leupeptin and 1 µM phosphoramidon) to a concentration of 5 to 15 µg/mL.

200 microlitres of this membrane fraction (contains 1 to 3 µg of protein) are incubated for 60 minutes at ambient temperature with 100 pM of ¹²⁵I-tyrosyl

10 melanin concentrating hormone (¹²⁵I-MCH commercially obtainable from NEN) and increasing concentrations of the test compound in a final volume of 250 microlitres. After the incubation the reaction is filtered using a cell harvester through 0.5% PEI treated glass fibre filters (GF/B, Unifilter Packard). The membrane-bound radioactivity retained on the filter is then determined after the 15 addition of scintillator substance (Packard Microscint 20) in a measuring device (TopCount of Packard).

The non-specific binding is defined as bound radioactivity in the presence of 1 micromolar MCH during the incubation period.

20

The analysis of the concentration binding curve is carried out on the assumption of one receptor binding site.

Standard:

Non-labelled MCH competes with labelled ¹²⁵I-MCH for the receptor binding with

25 an IC50 value of between 0.06 and 0.15 nM.

The KD value of the radioligand is 0.156 nM.

MCH-1 receptor-coupled Ca²⁺ mobilisation test

30

Method: Calcium mobilisation test with human MCH (FLIPR³⁸⁴)

Species: Human

Test cells: CHO/ Galpha 16 cells stably transfected with hMCH-R1
 Results: 1st measurement: % stimulation of the reference (MCH 10⁻⁶M)
 2nd measurement: pKB value

Reagents:	HBSS (10x)	(GIBCO)
	HEPES buffer (1M)	(GIBCO)
	Pluronic F-127	(Molecular Probes)
	Fluo-4	(Molecular Probes)
	Probenecid	(Sigma)
	MCH	(Bachem)
	bovine serum albumin (protease-free)	(Serva)
	DMSO	(Serva)
	Ham's F12	(BioWhittaker)
	FCS	(BioWhittaker)
	L-Glutamine	(GIBCO)
	Hygromycin B	(GIBCO)
	PENStrep	(BioWhittaker)
	Zeocin	(Invitrogen)

5

Clonal CHO/Galpah16 hMCH-R1 cells are cultivated in Ham's F12 cell culture medium (with L-glutamine; BioWhittaker; Cat.No.: BE12-615F). This contains per 500 ml 10% FCS, 1% PENStrep, 5 ml L-glutamine (200 mM stock solution), 3 ml hygromycin B (50 mg/mL in PBS) and 1.25 ml zeocin (100 µg/mL stock solution).

10 One day before the experiment the cells are plated on a 384-well microtitre plate (black-walled with a transparent base, made by Costar) in a density of 2500 cells per cavity and cultivated in the above medium overnight at 37°C, 5% CO₂ and 95% relative humidity. On the day of the experiment the cells are incubated with cell culture medium to which 2 mM Fluo-4 and 4.6 mM Probenecid have been added, at 37°C for 45 minutes. After charging with fluorescent dye the cells are washed four times with Hanks buffer solution (1 x HBSS, 20 mM HEPES), which is combined with 0.07% Probenecid. The test substances are diluted in Hanks buffer

15

solution, combined with 2.5% DMSO. The background fluorescence of non-stimulated cells is measured in the presence of substance in the 384-well microtitre plate five minutes after the last washing step in the FLIPR³⁸⁴ apparatus (Molecular Devices; excitation wavelength: 488 nm; emission wavelength: 5 bandpass 510 to 570 nm). To stimulate the cells MCH is diluted in Hanks buffer with 0.1% BSA, pipetted into the 384-well cell culture plate 35 minutes after the last washing step and the MCH-stimulated fluorescence is then measured in the FLIPR³⁸⁴ apparatus.

10 Data analysis:

1st measurement: The cellular Ca²⁺ mobilisation is measured as the peak of the relative fluorescence minus the background and is expressed as the percentage of the maximum signal of the reference (MCH 10⁻⁶M). This measurement serves to identify any possible agonistic effect of a test substance.
 15 2nd measurement: The cellular Ca²⁺ mobilisation is measured as the peak of the relative fluorescence minus the background and is expressed as the percentage of the maximum signal of the reference (MCH 10⁻⁶M, signal is standardised to 100%). The EC50 values of the MCH dosage activity curve with and without test substance (defined concentration) are determined graphically by the GraphPad Prism 2.01 curve program. MCH antagonists cause the MCH stimulation curve to shift to the right in the graph plotted.

20 \hookrightarrow The inhibition is expressed as a pKB value:

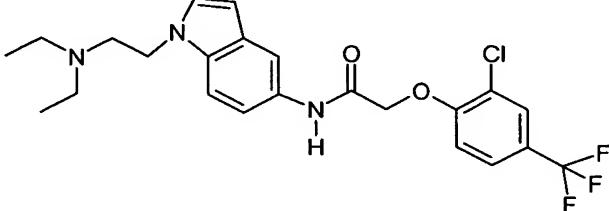
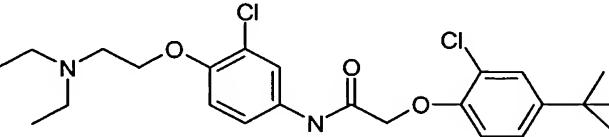
$$\text{pKB} = \log(\text{EC}_{50(\text{testsubstance+MCH})} / \text{EC}_{50(\text{MCH})} - 1) - \log C_{(\text{testsubstance})}$$

25

The compounds according to the invention, including the salts thereof, exhibit an MCH-receptor antagonistic activity in the tests mentioned above. Using the MCH-1 receptor binding test described above an antagonistic activity is obtained in a dosage range from about 10⁻¹⁰ to 10⁻⁵ M, particularly from 10⁻⁹ to 10⁻⁶ M.

30

The following IC₅₀ values were determined using the MCH-1 receptor binding test described above:

Compound according to Example no.	Structure	IC ₅₀ value
12		41 nM
34		17 nM

5

Some examples of formulations will be described hereinafter, wherein the term "active substance" denotes one or more compounds according to the invention, including the salts thereof. In the case of one of the combinations with one or more active substances described, the term "active substance" also includes the additional active substances.

Example A

15 Capsules for powder inhalation containing 1 mg active substance

Composition:

1 capsule for powder inhalation contains:

active substance	1.0 mg
------------------	--------

lactose	20.0 mg
hard gelatine capsules	<u>50.0 mg</u>
	71.0 mg

Method of preparation:

5 The active substance is ground to the particle size required for inhalation. The ground active substance is homogeneously mixed with the lactose. The mixture is packed into hard gelatine capsules.

Example B

10

Inhalable solution for Respimat® containing 1 mg active substance

Composition:

1 spray contains:

15	active substance	1.0 mg
	benzalkonium chloride	0.002 mg
	disodium edetate	0.0075 mg
	purified water ad	15.0 μ l

20 Method of preparation:

The active substance and benzalkonium chloride are dissolved in water and packed into Respimat® cartridges.

Example C

Inhalable solution for nebulisers containing 1 mg active substance

Composition:

5 1 vial contains:

active substance	0.1 g
sodium chloride	0.18 g
benzalkonium chloride	0.002 g
purified water ad	20.0 ml

10

Method of preparation:

The active substance, sodium chloride and benzalkonium chloride are dissolved in water.

15 Example D

Propellant type metered dose aerosol containing 1 mg active substance

Composition:

1 spray contains:

active substance	1.0 mg
lecithin	0.1 %
propellant gas ad	50.0 µl

Method of preparation:

25 The micronised active substance is homogeneously suspended in the mixture of lecithin and propellant gas. The suspension is transferred into a pressurised container with a metering valve.

Example E

Nasal spray containing 1 mg active substance

Composition:

5	active substance	1.0 mg
	sodium chloride	0.9 mg
	benzalkonium chloride	0.025 mg
	disodium edetate	0.05 mg
	purified water ad	0.1 ml

10

Method of preparation:

The active substance and the excipients are dissolved in water and transferred into a corresponding container.

15 Example F

Injectable solution containing 5 mg of active substance per 5 ml

Composition:

	active substance	5 mg
20	glucose	250 mg
	human serum albumin	10 mg
	glycofurol	250 mg
	water for injections ad	5 ml

25 Preparation:

Glycofurol and glucose are dissolved in water for injections (Wfi); human serum albumin is added; active ingredient is dissolved with heating; made up to specified volume with Wfi; transferred into ampoules under nitrogen gas.

Example G

Injectable solution containing 100 mg of active substance per 20 ml

5 Composition:

active substance 100 mg

monopotassium dihydrogen phosphate

= KH₂PO₄ 12 mg

disodium hydrogen phosphate

10 = Na₂HPO₄·2H₂O 2 mg

sodium chloride 180 mg

human serum albumin 50 mg

Polysorbate 80 20 mg

water for injections ad 20 ml

15

Preparation:

Polysorbate 80, sodium chloride, monopotassium dihydrogen phosphate and disodium hydrogen phosphate are dissolved in water for injections (WfI); human serum albumin is added; active ingredient is dissolved with heating; made up to specified volume with WfI; transferred into ampoules.

Example H

Lyophilisate containing 10 mg of active substance

25

Composition:

Active substance

Mannitol 300 mg

human serum albumin 20 mg

30

Preparation:

Mannitol is dissolved in water for injections (WfI); human serum albumin is added; active ingredient is dissolved with heating; made up to specified volume with WfI; transferred into vials; freeze-dried.

5

Solvent for lyophilisate:

Polysorbate 80 = Tween 80	20 mg
mannitol	200 mg
water for injections ad	10 ml

10

Preparation:

Polysorbate 80 and mannitol are dissolved in water for injections (WfI); transferred into ampoules.

15 Example I

Tablets containing 20 mg of active substance

Composition:

20	active substance	20 mg
	lactose	120 mg
	maize starch	40 mg
	magnesium stearate	2 mg
	Povidone K 25	18 mg

25

Preparation:

Active substance, lactose and maize starch are homogeneously mixed; granulated with an aqueous solution of Povidone; mixed with magnesium stearate; compressed in a tablet press; weight of tablet 200 mg.

30

Example J

Capsules containing 20 mg active substance

5 Composition:

active substance	20 mg
maize starch	80 mg
highly dispersed silica	5 mg
magnesium stearate	2.5 mg

10

Preparation:

Active substance, maize starch and silica are homogeneously mixed; mixed with magnesium stearate; the mixture is packed into size 3 hard gelatine capsules in a capsule filling machine.

15

Example K

Suppositories containing 50 mg of active substance

20 Composition:

active substance	50 mg
hard fat (Adeps solidus) q.s. ad	1700 mg

Preparation:

25 Hard fat is melted at about 38°C; ground active substance is homogeneously dispersed in the molten hard fat; after cooling to about 35°C it is poured into chilled moulds.

Example L

Injectable solution containing 10 mg of active substance per 1 ml

5 Composition:

active substance	10 mg
mannitol	50 mg
human serum albumin	10 mg
water for injections ad	1 ml

10

Preparation:

Mannitol is dissolved in water for injections (Wfl); human serum albumin is added;

active ingredient is dissolved with heating; made up to specified volume with Wfl;

15 transferred into ampoules under nitrogen gas.